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C3S 3A 3B 3C 5 7B 7D

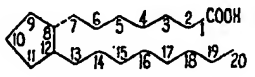
(19)

(54) IMPROVEMENTS IN OR RELATING TO PROSTAGLANDINS AND THE PREPARATION THEREOF

(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel organic compounds, and to methods for producing them. In particular, the several aspects of this invention relate to novel analogs of some of the known prostaglandins, for example, prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2), prostaglandin F_1 ($PGF_{1\alpha}$ and $PGF_{1\beta}$), prostaglandin F_2 ($PGF_{2\alpha}$ and $PGF_{2\beta}$), prostaglandin A_1 (PGA_1), prostaglandin A_2 (PGA_2), prostaglandin B_1 (PGB_1), prostaglandin B_2 (PGB_2), and the dihydro derivatives of PGE_1, $PGF_{1\alpha}$, $PGF_{1\beta}$, PGA_1, and PGB_1, and to novel methods for producing those novel prostaglandin analogs.

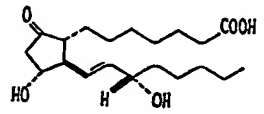
Each of the above-mentioned known prostaglandins is a derivative of prostanoic acid which has the following structure and atom numbering:



I

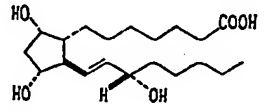
A systematic name for prostanoic acid is 7-[(2β-octyl)-cyclopent-1α-yl]heptanoic acid.

PGE_1 has the following structure:



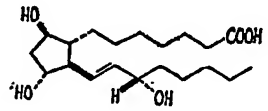
II

$PGF_{1\alpha}$ has the following structure:



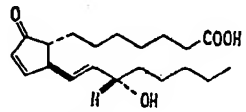
III

$PGF_{1\beta}$ has the following structure:



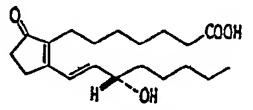
IV

PGA_1 has the following structure:



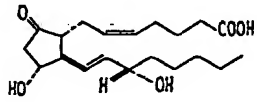
V

PGB_1 has the following structure:

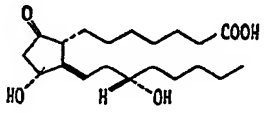


VI

Each of the known prostaglandins PGE_2, $PGF_{2\alpha}$, $PGF_{2\beta}$, PGA_2, and PGB_2 has a structure the same as that shown for the corresponding PG_1 compound except that in each, C-5 and C-6 are linked with a *cis* carbon-carbon double bond. For example, PGE_2 has the following structure:



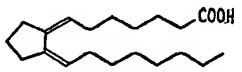
Each dihydro derivative of PGE_1, $PGF_{1\alpha}$, $PGF_{1\beta}$, PGA_1, and PGB_1 has a structure the same as that shown for the corresponding PG_1 compound except that in each, C-13 and C-14 are linked with a carbon-carbon single bond. For example, dihydro-PGE_1 has the following structure:



The prostaglandin formulas mentioned above each have several centers of asymmetry. Each formula represents the particular optically active form of the prostaglandin obtained from certain mammalian tissues, for example, sheep vesicular glands, swine lung, and human seminal plasma, or by reduction or dehydration of a prostaglandin so obtained. See, for example, Bergstrom et al., Pharmacol. Rev. 20, 1 (1968), and references cited therein. The mirror image of each formula represents a molecule of the enantiomer of that prostaglandin. The racemic form of the prostaglandin consists of equal numbers of two types of molecules, one represented by one of the above formulas and the other represented by the mirror image of that formula. Thus, both formulas are needed to define a racemic prostaglandin. See Nature 212, 38 (1966) for discussion of the stereo-chemistry of the prostaglandins.

In formulas I, II, III, IV, V and VI, as well as in the formulas given hereinafter, broken line attachments to the cyclopentane ring indicate substituents in alpha configuration, i.e., below the plane of the cyclopentane ring. Heavy solid line attachments to the cyclopentane ring indicate substituents in beta configuration, i.e., above the plane of the cyclopentane ring.

Prostaglandins with carboxyl-terminated side chains attached to the cyclopentane ring in beta configuration are also known. These are derivatives of 8-iso-prostanoic acid which has the following formula:



VII

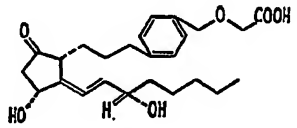
A systematic name for 8-iso-prostanoic acid is 7-[(2β-octyl)-cyclopent-1β-yl]hephanoic acid.

The novel prostaglandin analogs of this invention each have an oxa oxygen (—O—) and a divalent phenylene radical

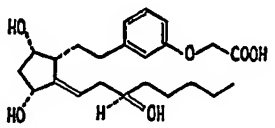
in the carboxyl-terminated side chain of the prostanoic acid structure (I) or the 8-iso-prostanoic aicd structure (VII). These divalent groups are located between the carboxyl group and the cyclopentane ring, and are either in addition to the six methylene radicals of said chain or in place of one to five of said methylene radicals. Bonding to the phenylene ring is either ortho, meta, or para. The oxa group is between the phenylene radical and the carboxyl group.

Some of the novel prostaglandin analogs of this invention also have, in addition, a benzene ring as part of the C-13 to C-20 chain of the prostanoic acid structure (I) or 8-iso-prostanoic acid structure (VII). That benzene ring is present as a substituted or unsubstituted phenyl radical attached as a substituent to one of the methylenes between C-15 and the terminal methyl of the prostanoic acid or 8-isoprostanoic acid structure. Alternatively, the substituted or unsubstituted phenyl radical is attached to the terminal or omega carbon of the C-16 to C-20 portion of the chain, replacing one of the hydrogens of the terminal methyl, the entire terminal methyl, or the terminal methyl plus one to four of the methylenes adjacent to that terminal methyl.

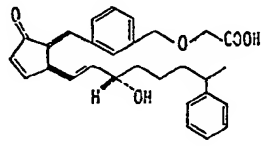
For example, five of the novel prostaglandin analogs of this invention are represented by the formulas:



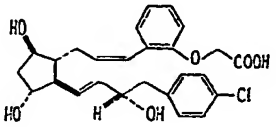
VIII



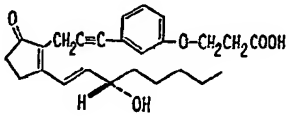
IX



X



XI



XII

Based on its relationship to PGE_1 and prostanoic acid, the compound of Formula VIII is named 3-oxa-4,5-*inter-p*-phenylene-PGE_1. Similarly, the compound of Formula IX is named 13,14 - dihydro - 15 - beta - 3 - oxa - 3,6 - *inter* - *m* - phenylene - 4,5 - di - nor - $PGF_{1\alpha}$, the compound of Formula X is named 8 - iso - 3 - oxa - 19 - phenyl - 4,7 - *inter* - *m* - phenylene - 5,6 - dinor - PGA_1, the compound of Formula XI is named 3 - oxa - 16 - (4 - chlorophenyl) - 3,5 - *inter* - *o* - phenylene - 4,17,18,19,20 - pentanor - $PGF_{2\beta}$, and the compound of Formula XII is named 5,6-dehydro-4-oxa-4,5-*inter-m*-phenylene-PGB_2.

These names for the compounds of Formulas VIII to XII are typical of the names used hereinafter for the novel compounds of this invention. These names can better be understood by reference to the structure and numbering system of prostanoic acid (Formula I, above). That formula has seven carbon atoms in the carboxy-terminated chain and eight carbon atoms in the hydroxy-containing chain. In these names, "3-oxa" and "4-oxa" indicate an oxa oxygen (—O—) in place of the 3-methylene and 4-methylene, respectively of the PG compound.

The use of "nor", "dinor", "trinor", "tetranor", "pentanor", and "hexanor" in the names for the novel compounds of this invention indicates the absence of one or more of the chain carbon atoms and the attached hydrogen atoms. The number or numbers in front of nor, dinor, etc., indicate which of the original prostanoic acid carbon atoms are missing in the named compound.

Each of the names of the novel compounds of this invention contains (*inter-p*-phenylene), (*inter-m*-phenylene), or (*inter-o*-phenylene), preceded by two numbers. That indicates that *p*-phenylene, *m*-phenylene, or *o*-phenylene has been inserted between (*inter*) the two carbon atoms so numbered in the formula of prostanoic acid.

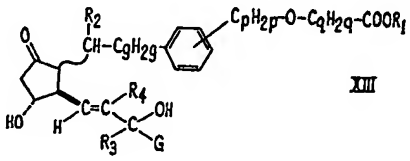
Thus, Formula X differs from iso-prostanoic acid in that an oxa oxygen replaces carbon 3, carbons 5 and 6 of prostanoic acid are missing, *m*-phenylene has been inserted between carbons 4 and 7 of prostanoic acid, and a phenyl has been attached to carbon 19 of prostanoic acid. Formula X also, of course, is an A type prostaglandin, having a carbonyl oxygen and a 10:11 double bond.

Novel compounds of this invention with the carboxyl-terminated chain attached to the cyclopentane ring in beta configuration are 8-iso compounds (Formula VII), and are so designated by using "8-iso" in the name. An example is the name given above for the compound of Formula X. If 8-iso does not appear in the name, attachment of the carboxy-terminated chain in alpha configuration is to be assumed.

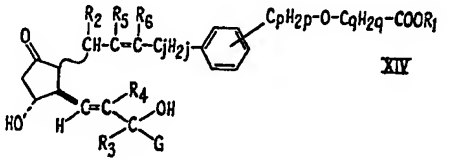
Novel compounds of this invention with epi configuration for the hydroxy at C-15 are so designated by using "15-beta" in the name. An example is the name given above for the compound of Formula IX. If 15-beta does not appear in the name, the natural configuration for the C-15 hydroxy, identified as the "S" configuration for PGE_1, is to be assumed.

Some of the novel compounds of this invention differ structurally in other ways from the known prostanoic acid derivatives, having for example, more or fewer carbon atoms in either chain, and having one or more alkyl and/or fluoro substitutents in the chains.

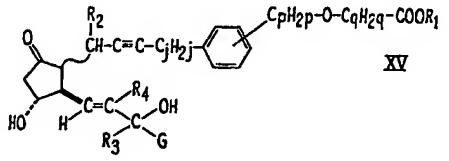
The following formulas represent the novel oxaphenylene compounds of this invention.



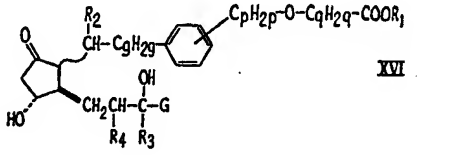
XIII



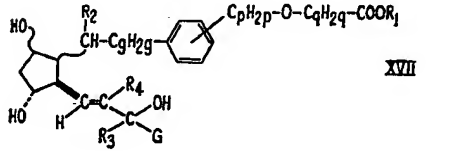
XIV



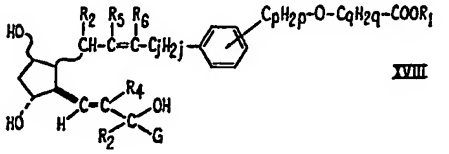
XV



XVI



XVII



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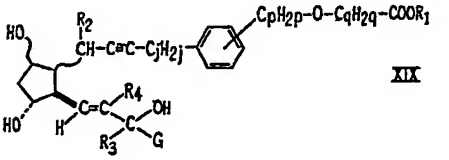

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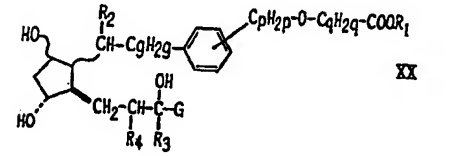

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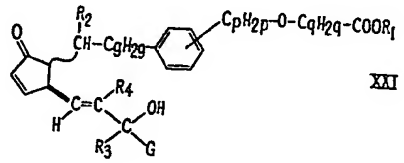
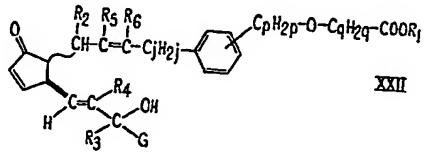
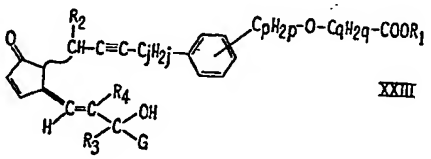


XXI



XXII



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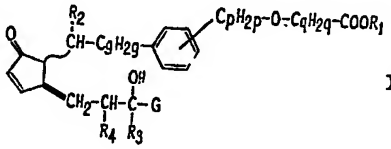
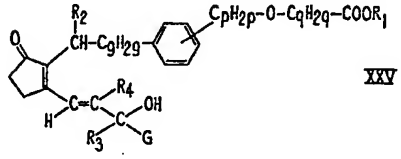
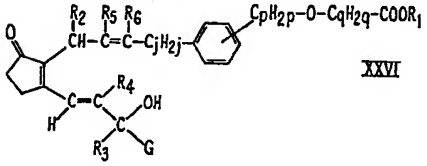


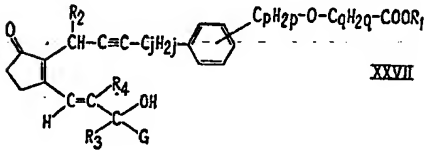
XXIV



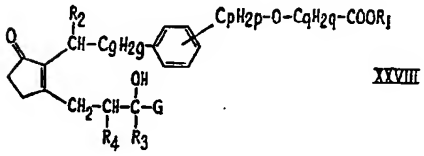
XXV



XXVI



XXVII



XXVIII

Formulas XIII, XIV, XV and XVI represent oxa-phenylene compounds of the PGE type. Formulas XVII, XVIII, XXIX, and XX represent oxa-phenylene compounds of the PGF type. Formulas XXI, XXII, XXIII, and XXIV represent oxaphenylene compounds of the PGA type. Formulas XXV, XXVI, XXVII, and XXVIII represent oxa-phenylene compounds of the PGB type.

In Formulas XIII to XXVIII, R_1 is hydrogen, alkyl of one to 8 carbon atoms, inclusive, cycloalkyl of 3 to 10 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, phenyl substituted with one to 3 chloro or alkyl of one to 4 carbon atoms, inclusive, or ethyl substituted in the β-position with 3 chloro, 2 or 3 bromo, or 1, 2, or 3 iodo. R_2, R_3, R_4, R_5, and R_6 are hydrogen or alkyl of one to 4 carbon atoms, inclusive.

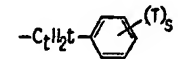
In Formulas XIII to XXVIII, C_qH_{2q} represents alkylene of one to 6 carbon atoms, inclusive, with one, 2, or 3 carbon atoms between —O— and —$COOR_1$; C_pH_{2p} represents a valence bond or alkylene of one to 6 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between the ring and the —O—.

In Formulas XIII, XVI, XVII, XX, XXI, XXIV, XXV, and XXVIII, C_gH_{2g} represents a valence bond, i.e., wherein g is zero, or alkylene of one to 8 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between —CHR_2— and the ring. C_gH_{2g}, C_pH_{2p}, and C_qH_{2q} together represent one to 20 carbon atoms, inclusive, with total chain lengths of one to 5 carbon atoms, inclusive.

In Formulas XIV, XV, XVIII, XIX, XXII, XXIII, XXVI, and XXVII, C_jH_{2j} represents a valence bond, i.e., wherein j is zero, or alkylene of one to 5 carbon atoms, inclusive, with one or 2 carbon atoms between =CR_6—, or ≡C— and the ring, with the proviso that the total carbon-atom content of —CR_5=CR_6—C_jH_{2j}— does not exceed 8, C_jH_{2j}, C_pH_{2p}, and C_qH_{2q} together representing one to 17 carbon atoms, inclusive, with total chain lengths one to 3 carbon atoms, inclusive.

In other words, regarding the meaning of C_gH_{2g}, C_jH_{2j}, C_pH_{2p}, and C_qH_{2q} as defined above, the novel compounds of this invention include compounds wherein a carbon atom of the phenylene radical is attached directly to —CHR_2— or to =CR_6—, or is ≡C— in ortho, meta, or para orientation relative to the oxa-containing portion of the carboxyl chain. When C_gH_{2g} represents alkylene, the chain of carbon atoms which connects —CHR_2 to a carbon atom of phenylene will be one, 2, 3, or 4 carbon atoms long. When C_jH_{2j} represents alkylene, the chain of carbon atoms which connects =CR_6— or ≡C— to a carbon atom of phenylene will be one or 2 carbon atoms long. C_pH_{2p} represents a valence bond or alkylene of one to 6 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between the ring and the —O—. C_qH_{2q} always represents alkylene, i.e., —$COOR_1$ is not attached directly to the oxa group, the alkylene chain being one, 2, or 3 carbon atoms long. Any or all of these alkylene chains are unsubstituted or substituted with alkyl carbons in the form of one or more alkyl groups within the total carbon content of each chain as specified above, i.e., 8 carbons for C_gH_{2g}, 5 carbons for C_jH_{2j}, 6 carbons for C_pH_{2p}, and 6 carbons for C_qH_{2q}. When C_gH_{2g} or C_jH_{2j} is alkylene, it is the same as or different than C_pH_{2p} or C_qH_{2q}, 20 carbon atoms being the maximum total carbon content and 5 carbon atoms being the maximum total chain length for the combination of C_gH_{2g}, C_pH_{2p}, and C_qH_{2q}, and 17 carbon atoms being the maximum total carbon content and 3 carbon atoms being the maximum total chain length for the combination of C_jH_{2j}, C_pH_{2p}, and C_qH_{2q}. The latter combination is subject to the proviso that the total carbon atom content of —CR_5=CR_6—C_jH_{2j}—, wherein R_5 and R_6 are hydrogen or alkyl of one to 4 carbon atoms, inclusive, does not by itself exceed 8. To illustrate these definitions, when C_gH_{2g} is trimethylene, C_pH_{2p} and C_qH_{2q} are methylene, or one of them is a valence bond and tthe other is ethylene, either of those with alkyl substituents, but not both as ethylene.

In Formulas XIII to XXVIII, G represents hydrogen; alkyl of one to 10 carbon atoms, inclusive, substituted with zero, one, 2, or 3 fluoro; alkyl of 2 to 10 carbon atoms, inclusive, substituted with 4 or 5 fluoro on the omega and omega-minus-one carbon atoms; or a monovalent radical of the formula



wherein C_tH_{2t} represents a valence bond or alkylene of one to 10 carbon atoms, inclusive, substituted with zero, one, or 2 fluoro, with one to 7 carbon atoms, inclusive, between —CR_3OH— and the ring; wherein T is alkyl of one to 4 carbon atoms, inclusive, fluoro, chloro, trifluoromethyl, or —OR_9, wherein R_9 is hydrogen, alkyl of one to 4 carbon atoms, inclusive, or 2-tetrahydropyranyl, and s is zero, one, 2, or 3, with the proviso that not more than two T's are other than alkyl and when two or three T's are present as substituents they may be the same or different.

The wavy line ~ in Formulas XIII to XXVIII indicates attachment of the group

to the ring in alpha or beta configuration. In the case of the compounds of Formulas XVII, XVIII, XIX, and XX, there are two wavy lines, and those formulas encompass compounds wherein the configurations of the hydroxy and the carboxyl-terminated radicals are, respectively, α,α, α,β, β,α, and β,β.

Formulas XIII to XXVIII include lower alkanoates i.e. derived from alkanoic acids of 1 to 8 carbon atoms, inclusive and also pharmacologically acceptable salts when R_1 is hydrogen.

Also included in Formulas XIII to XXVIII are separate isomers wherein the side chain hydroxy is in α or β (natural or epi) configuration.

Included in Formulas XIV, XVIII, XXII, and XXVI, are both the *cis* and the *trans* compounds with respect to the carbon-carbon double bond in the carboxyl-terminated side chain. In all of the compounds containing —CH=CR$_4$—, that carbon-carbon double bond is in *trans* configuration, and the chain containing R_4 is attached to the cyclopentane or cyclopentene ring in beta configuration in compounds encompassed by Formulas XIII to XXIV.

The novel oxa-phenylene compounds of this invention include racemic compounds and both optically active enantiomeric forms thereof. As discussed hereinabove, two structural formulas are required to define accurately these racemic compounds. For convenience, only a single structural formula is used, for example, Formulas XIII to XXVIII, to define the racemic form and both enantiomeric forms of each group of novel prostaglandin analogs. Each formula is, however, to be construed as including said racemic forms and both of said optically active enantiomeric forms.

Formula XIII represents 3-oxa-4,5-*inter*-*p*-phenylene-PGE$_1$ (Formula VIII hereinabove) when R_1, R_2, R_3, and R_4 are each hydrogen, C_gH_{2g} is ethylene, C_pH_{2p} is methylene, C_qH_{2q} is methylene, C_gH_{2g} and C_pH_{2p} are attached to the phenylene in para orientation, G is n-pentyl, the carboxyl-terminated side chain is attached to the cyclopentane ring in alpha configuration, and the configuration of the side chain hydroxy is alpha.

With regard to Formulas XIII to XXVIII, examples of alkyl of one to 4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, and isomeric forms thereof. Examples of alkyl of one to 8 carbon atoms, inclusive, are those given above, and pentyl, hexyl, heptyl, octyl, and isomeric forms thereof. Examples of alkyl of one to 10 carbon atoms, inclusive, are those given above, and nonyl, decyl, and isomeric forms thereof. Examples of cycloalkyl of 3 to 10 carbon atoms, inclusive, which includes alkyl-substituted cycloalkyl, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, 2,3,4-triethylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, 3-pentylcyclopentyl, 3-tert-butylcyclopentyl, cyclohexyl, 4-tert-butylcyclohexyl, 3-isopropylcyclohexyl, 2,2-dimethylcyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl. Examples of aralkyl of 7 to 12 carbon atoms, inclusive, are benzyl, phenethyl, 1-phenylethyl, 2-phenylpropyl, 4-phenylbutyl, 3-phenylbutyl, 2-(1-naphthylethyl), and 1-(2-naphthylmethyl). Examples of phenyl substituted by one to 3 chloro or alkyl of one to 4 carbon atoms, inclusive, are *p*-chlorophenyl, *m*-chlorophenyl, *o*-chlorophenyl, 2,4-dichlorophenyl, 2,4,6-trichlorophenyl, *p*-tolyl, *m*-tolyl, *o*-tolyl, *p*-ethylphenyl, *p*-tert-butylphenyl, 2,5-dimethylphenyl, 4-chloro-2-methylphenyl, and 2,4-dichloro-3-methylphenyl.

Examples of alkyl of one to 10 carbon atoms, inclusive, substituted with one to 3 fluoro, are 2-fluoroethyl, 2-fluorobutyl, 3-fluorobutyl, 4-fluorobutyl, 5-fluoropentyl, 4-fluoro-4-methylpentyl, 3-fluoroisoheptyl, 8-fluorooctyl, 3,4-difluorobutyl, 4,4-difluoropentyl, 5,5-difluoropentyl, 5,5,-trifluoropentyl, and 10,10,10-trifluorodecyl.

Examples of alkyl of 2 to 10 carbon atoms substituted with 4 or 5 fluoro on the omega and omega-minus-one carbon atoms are 1,2,2,2-tetrafluoroethyl, 1,1,2,2,2-pentafluoroethyl, 3,3,4,4-tetrafluorobutyl, 3,3,4,4,4 - pentafluorobutyl, 4,4,5,5-tetrafluoropentyl, 4,5,5,5-tetrafluoropentyl, 4,4,5,5,5-pentafluoropentyl, 6,6,7,7,7-pentafluoroheptyl and 9,9,10,10,10-pentafluorodecyl.

Examples of alkylene within the various scopes of C_gH_{2g}, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and C_tH_{2t}, as those are defined above, are methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, and heptamethylene, and those alkylene with one or more alkyl substituents on one or more carbon atoms thereof, e.g., —CH(CH$_3$)—,

—C(CH$_3$)$_2$—, —CH(CH$_2$CH$_3$)—, —CH$_2$—CH(CH$_3$)—, —CH(CH$_3$)—CH(CH$_3$)—,

—CH$_2$—C(CH$_3$)$_2$—, —CH$_2$—CH(CH$_3$)—CH$_2$—,

—CH$_2$—CH$_2$—CH(CH$_2$CH$_2$CH$_3$)—, —CH(CH$_3$)—CH(CH$_3$)—CH$_2$—CH$_2$—,

$$—CH_2—CH_2—CH_2—C(CH_3)_2—CH_2—,$$

$$—CH_2—CH_2—CH_2—CH_2—CH(CH_3)—,$$

$$—CH_2—CH_2—CH_2—CH_2—CH_2—C(CH_3)_2—,$$

$$—CH(CH_3)—CH_2—CH(CH_3)—CH_2—CH_2—CH(CH_3)—,$$

and

$$—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—C(CH_3)_2—.$$

Examples of alkylene substituted with one or 2 fluoro and within the scope of C_tH_{2t}, as defined above, are —CHF—CH_2—, —CHF—CHF—,

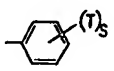
$$—CH_2—CH_2—CF_2—, —CH_2—CHF—CH_2—, —CH_2—CH_2—CF(CH_3)—,$$

$$—CH_2—CH_2—CH_2—CF_3—,$$

and

$$—CHF—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—.$$

Examples of



as defined above are phenyl, *p*-tolyl, *m*-tolyl, *o*-tolyl, *p*-fluorophenyl, *m*-fluorophenyl, *o*-fluorophenyl, *p*-chlorophenyl, *m*-chlorophenyl, *o*-chlorophenyl, *p*-trifluoromethylphenyl, *m*-trifluoromethylphenyl, *p*-trifluoromethylphenyl, *p*-hydroxyphenyl, *m*-hydroxyphenyl, *o*-hydroxyphenyl, *p*-methoxyphenyl, *m*-methoxyphenyl, *m*-methoxyphenyl, *o*-methoxyphenyl, *p*-tetrahydropyran-2-yloxyphenyl, *m*-tetrahydropyran-2-yloxyphenyl, *o*-tetrahydropyran-2-yloxyphenyl, *o*-ethylphenyl, *m*-isopropylphenyl, *p*-tert-butylphenyl, *p*-butoxyphenyl, 3,4-dimethylphenyl, 2,4-diethylphenyl, 2,4,6-trimethylphenyl, 3,4,5-trimethylphenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 2-chloro-4-methylphenyl, 2-fluoro-4-methoxyphenyl, 3,5-dimethyl-4-fluorophenyl, 2,6-dimethyl-4-hydroxyphenyl, and 2,4-di(trifluoromethyl)phenyl.

PGE_1, PGE_2, dihydro-PGE_1, and the corresponding PGF_α, PGF_β, PGA, and PGB compounds, and their esters, acylates, and pharmacologically acceptable salts, are extremely potent in causing various biological responses. For that reason, these compounds are useful for pharmacological purposes. See, for example, Bergstrom et al., Pharmacol. Rev. 20, 1 (1968), and references cited therein. A few of those biological responses are systemic arterial blood pressure lowering in the case of the PGE, PGF_β, and PGA compounds as measured, for example, in anesthetized (pentobarbital sodium) pentolinium-treated rats with indwelling aorticand right heart cannulas; stimulation of smooth muscle as shown, for example, by tests on strips of guinea pig ileum, rabbit duodenum, or gerbil colon; potentiation of other smooth muscle stimulants; antilipolytic activity as shown by antagonism of epinephrine-induced mobilization of free fatty acids or inhibition of the spontaneous release of glycerol from isolated rat fat pads; inhibition of gastric secretion in the case of the PGE and PGA compounds as shown in dogs with secretion stimulated by food or histamine infusion; activity on the central nervous system; decrease of blood platelet adhesiveness as shown by platelet-to-glass adhesiveness, and inhibition of blood platelet aggregation and thrombus formation induced by various physical stimuli, e.g., arterial injury, and various biochemical stimuli, e.g., ADP, ATP, serotonin, thrombin, and collagen; and in the case of the PGE and PGB compounds, stimulation of epidermal proliferation and keratinization as shown when applied in culture to embryonic chick and rat skin segments.

Because of these biological responses, these known prostaglandins are useful to study, prevent, control, or alleviate a wide variety of diseases and undesirable physiological conditions in birds and mammals, including humans, useful domestic animals, pets, and zoological specimens, and in laboratory animals, for example, mice, rats, rabbits, and monkeys.

For example, these compounds, and especially the PGE compounds, are useful in mammals, including man, as nasal decongestants. For this purpose, the compounds are used in a dose range of 10 μg. to 10 mg. per ml. of a pharmacologically suitable liquid vehicle or as an aerosol spray, both for topical application.

The PGE and PGA compounds are useful in mammals, including man and certain useful animals, e.g., dogs and pigs, to reduce and control excessive gastric secretion, thereby reducing or avoiding gastrointestinal ulcer formation, and accelerating the healing of such ulcers already present in the gastrointestinal tract. For this purpose, the compounds are injected or infused intravenously, subcutaneously, or intramuscularly in an infusion dose range 0.1 μg. to 500 μg. per kg. of body weight per minute, or in a total daily dose by injection or infusion in the range 0.1 to 20 mg. per kg. of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The PGE, PGF_α, and PGF_β compounds are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, and to remove or prevent the formation of thrombi in mammals, including man, rabbits, and rats. For example, these compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent post-operative thrombosis, to promote patency of vascular grafts following surgery, and to treat conditions such as atherosclerosis, arterosclerosis, blood clotting defects due to lipemia, and other clinical conditions in which the underlying etiology is associated with lipid imbalance or hyperlipidemia. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response, especially in emergency situation, the intravenous route of administration is preferred. Doses in the range 0.005 to 20 mg. per kg. of body weight per day are used, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The PGE, PGF_α, and PGF_β compounds are especially useful as additives to blood, blood products, blood substitutes, and other fluids which are used in artificial extracorporeal circulation and perfusion of isolated body portions, e.g., limbs and organs, whether attached to the original body, detached and being preserved or prepared for transplant, or attached to a new body. During these circulations and perfusions, aggregated platelets tend to block the blood vessels and portions of the circulation apparatus. This blocking is avoided by the presence of these compounds. For this purpose, the compound is added gradually or in single or multiple portions to the circulating blood, to the blood of the donor animal, to the perfused body portion, attached or detached, to the recipient, or to two or all of those at a total steady state dose of .001 to 10 mg. per liter of circulating fluid. It is especially useful to use these compounds in laboratory animals, e.g., cats, dogs, rabbits, monkeys, and rats, for these purposes in order to develop new methods and techniques for organ and limb transplants.

PGE compounds are extremely potent in causing stimulation of smooth muscle, and are also highly active in potentiating other known smooth muscle stimulators, for example, oxytocic agents, e.g., oxytocin, and the various ergot alkaloids including derivatives and analogs thereof. Therefore, PGE_2, for example, is useful in place of or in combination with less than usual amounts of these known smooth muscle stimulators, for example, to relieve the symptoms of paralytic ileus, or to control or prevent atonic uterine bleeding after abortion or delivery, to aid in expulsion of the placenta, and during the puerperium. For the latter purpose, the PGE compound is administered by intravenous infusion immediately after abortion or delivery at a dose in the range 0.01 to 50 μg. per kg. of body weight per minute until the desired effect is obtained. Subsequent doses are given by intravenous, subcutaneous, or intramuscular injection or infusion during puerperium in the range 0.01 to 2 mg. per kg. of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal.

The PGE, PGA, and PGF_β compounds are useful as hypotensive agents to reduce blood pressure in mammals, including man. For this purpose, the compounds are administered by intravenous infusion at the rate 0.01 to 50 μg. per kg. of body weight per minute, or in single or multiple doses of 25 to 500 μg. per kg. of body weight total per day.

The PGE, PGF_α, and PGF_β compounds are useful in place of oxytocin to induce labor in pregnant female animals, including man, cows, sheep, and pigs, at or near term, or in pregnant animals with intrauterine death of the fetus from about 20 weeks to term. For this purpose, the compound is infused intravenously at a dose of 0.01 to 50 μg. per kg. of body weight per minute until or near the termination of the second stage of labor, i.e., expulsion of the fetus. These compounds are especially useful when

the female is one or more weeks post-mature and natural labor has not started, or 12 to 60 hours after the membranes have ruptured and natural labor has not yet started. An alternative route of administration is oral.

The PGE, PGF_{α}, and PGF_{β} compounds are useful for controlling the reproductive cycle in ovulating female mammals, including humans and animals such as monkeys, rats, rabbits, dogs, and cattle. By the term ovulating female mammals is meant animals which are mature enough to ovulate but not so old that regular ovulation has ceased. For that purpose, $PGF_{2\alpha}$, for example, is administered systemically at a dose level in the range 0.01 mg. to 20 mg. per kg. of body weight of the female mammal, advantageously during a span of time starting approximately at the time of ovulation and ending approximately at the time of menses or just prior to menses. Intravaginal and intrauterine are alternative routes of administration. Additionally, expulsion of an embryo or a fetus is accomplished by similar administration of the compound during the first third of the normal mammalian gestation period.

As mentioned above, the PGE compounds are potent antagonists of epinephrine-induced mobilization of free fatty acids. For this reason, this compound is useful in experimental medicine for both *in vitro* and *in vivo* studies in mammals, including man, rabbits, and rats, intended to lead to the understanding, prevention, symptom alleviation, and cure of diseases involving abnormal lipid mobilization and high free fatty acid levels, e.g., diabetes mellitus, vascular diseases, and hyperthyroidism.

The PGA compounds and derivatives and salts thereof increase the flow of blood in the mammalian kidney, thereby increasing volume and electrolyte content of the urine. For that reason, PGA compounds are useful in managing cases of renal disfunction, especially in cases of severely impared renal blood flow, for example, the hepatorenal syndrome and early kidney transplant rejection. In cases of excessive or inappropriate ADH (antidiuretic hormone; vasopressin) secretion, the diuretic effect of these compounds is even greater. In anephretic states, the vasopressin action of these compounds is especially useful. Illustratively, the PGA compounds are useful to alleviate and correct cases of edema resulting, for example, from massive surface burns, and in the management of shock. For these purposes, the PGA compounds are preferably first administered by intravenous injection at a dose in the range 10 to 1000 μg. per kg. of body weight or by intravenous infustion at a dose in the range 0.1 to 20 μg. per kg. of body weight per minute until the desired effect is obtained. Subsequent doses are given by intravenous, intramuscular, or subcutaneous injection or infusion in the range 0.05 to 2 mg. per kg. of body weight per day.

The PGE and PGB compounds promote and accelerate the growth of epidermal cells and keratin in animals, including humans, useful domestic animals, pets, zoological specimens, and laboratory animals. For that reason, these compounds are useful to promote and accelerate healing of skin which has been damaged, for example, by burns, wounds, and abrasions, and after surgery. These compounds are use useful to promote and accelerate adherence and growth of skin autografts, especially small, deep (Davis) grafts which are intended to cover skinless areas by subsequent outward growth rather than initially, and to retard rejection of homografts.

For these purposes, these compounds are preferably administered topically at or near the site where cell growth and keratin formation is desired, advantageously as an aerosol liquid or micronized powder spray, as an isotonic aqueous solution in the case of wet dressings, or as a lotion, cream, or ointment in combination with the usual pharmaceutically acceptable diluents. In some instances, for example, when there is substantial fluid loss as in the case of extensive burns or skin loss due to other causes, systemic administration is advantageous, for example, by intravenous injection or infution, separate or in combination with the usual infusions of blood, plasma, or substitutes thereof. Alternative routes of administration are subcutaneous or intramuscular near the site, oral, sublingual, buccal, rectal, or vaginal. The exact dose depends on such factors as the route of administration, and the age, weight, and condition of the subject. To illustrate, a wet dressing for topical application to second and/or third degree burns of skin area 5 to 25 square centimeters would advantageously involve use of an isotonic aqueous solution containing 1 to 500 μg./ml. of the PGB compound or several times that concentration of the PGE compound. Especially for topical use, these prostaglandins are useful in combination with antibiotics, for example, gentamycin, neomycin, polymyxin B, bacitracin, spectinomycin, and oxytetracycline, with other antibacterials, for example, mafenide hydrochloride, sulfadiazine, furazolium chloride, and nitrofurazone, and with corticoid steroids, for example, hydrocortisone, prednisolone, methylprednisolone, and fluprednisolone, each of those being used in the combination at the usual concentration suitable for its use alone.

The novel Formula XIII, XIV, XV and XVI PGE-type oxa-phenylene com-

pounds, the novel Formula XVII, XVIII, XIX, and XX PGF_α-type and PGF_β-type oxa-phenylene compounds, the novel Formula XXI, XXII, XXIII, and XIV PGA-type oxaphenylene compounds, and the novel Formula XXV, XXVI, XXVII, and XXVIII PGB-type oxa-phenylene compounds each cause the biological responses described above for the PGE, PGF_α, PGF_β, PGA, and PGB compounds, respectively, and each of these novel compounds is accordingly useful for the above-described corresponding purposes, and is used for those purposes in the same manner as described above.

The known PGE, PGF_α, PGF_β, PGA, and PGB compounds uniformly cause multiple biological responses even at low doses. For example, PGE_1 and PGE_2 both cause vaso-depression and smooth muscle stimulation at the same time they exert anti-lipolytic activity. Moreover, for many applications, these known prostaglandins have an inconveniently short duration of biological activity. In striking contrast, the novel prostaglandin analogs of Formulas XIII to XXVIII are substantially more specific with regard to potency in causing prostaglandin-like biological responses, and have a substantially longer duration of biological activity. Therefore, each of these novel prostaglandin analogs is useful in place of one of the corresponding above-mentioned known prostaglandins for at least one of the pharmacological purposes indicated above for the latter, and is surprisingly and unexpectedly more useful for that purpose because it has a different and narrower spectrum of biological activity than the known prostaglandin, and therefore is more specific in its activity and causes smaller and fewer undesired side effects than the known prostaglandin. Moreover, because of its prolonged activity, fewer and smaller doses of the novel prostaglandin analog can frequently be used to attain the desired result.

To obtain the optimum combination of biological response specificity, potency, and duration of activity, certain compounds within the scope of Formula XIII to XXVIII are preferred. For example, in compounds of Formulas XIII, XVI, XVII, XX, XXI, XXIV, XXV, and XXVIII, it is preferred that the carboxyl-terminated side chain contain a total of 2 to 4 chain carbon atoms, inclusive, excluding the phenylene and $—COOR_1$, and including $—CHR_2—$. In other words, preferred compounds of these formulas are those wherein C_gH_{2g}, C_pH_{2p}, and C_qH_{2q} together represent one, 2, or 3 chain carbon atoms. Especially preferred compounds of these formulas are those wherein C_gH_{2g}, and C_pH_{2p} each represent a valence bond, and C_qH_{2q} represents one or two chain carbon atoms, especially methylene or ethylene, and those wherein C_gH_{2g} represents a valence bond, and C_pH_{2p} and C_qH_{2q} each represent a single chain carbon atom, especially methylene.

In compounds of Formulas XIV, XV, XVIII, XIX, XXII, XXIII, XXVI, and XXVII, it is preferred that the carboxyl-terminated side chain contain a total of 4 or 5 chain carbon atoms, excluding the phenylene and $—COOR_1$, and including $—CHR_2—CR_5=CR_6—$ and $—CHR_2—C\equiv C—$. In other words, preferred compounds of these formulas are those wherein C_jH_{2j}, C_pH_{2p}, and C_qH_{2q} together represent one or 2 chain carbon atoms. Included in these compounds are those wherein C_jH_{2j} and C_pH_{2p} each represent a valence bond, and C_qH_{2q} represents one or two chain carbon atoms, especially methylene or ethylene, and those wherein C_jH_{2j} represents a valence bond, and C_pH_{2p} and C_qH_{2q} each represent a single chain carbon atom, especially methylene.

As used herein, a chain carbon atom is part of the direct chain of carbon atoms linking $—CHR_2—$ or $=CR_6—$ to the phenylene, the phenylene to the oxa, and the oxa to $—COOR_1$. Thus, the chain $—CH(CH_3)—C(CH_3)_2—$ contains 5 carbon atoms but only 2 chain atoms.

Another preference for the carboxy-terminated side chain in compounds of Formulas XIII to XXIV is that the phenylene be a meta-phenylene.

Another preference for the compounds of Formulas XIII to XXVIII is that R_2, R_3, R_4, R_5, and R_6 are hydrogen or methyl. All of those R groups can be hydrogen, all can be methyl, or there can be any of the possible combinations of hydrogen and methyl.

Certain variations in the nature of G in the compounds of Formulas XIII to XXVIII are especially important. In the known prostaglandins, e.g., PGE_1, the portion of the molecule corresponding to G in Formulas XIII to XXVIII is n-pentyl. When G is unsubstituted alkyl or fluoro-substituted alkyl as defined above, there are two alternative preferences which result in compounds with optimum combinations of biological properties. One preference is that G is straight chain alkyl of 3 to 7 carbon atoms, inclusive, with or without a fluoro substituent at the 1-position, e.g., $—CHF—(CH_2)_a—CH_3$, wherein a is one, 2, 3, 4, or 5. Especially preferred among these are n-pentyl and 1-fluoropentyl. The other preference, especcially when prolonged duration of biological activity is desired, is that there be alkyl branching or fluoro substituents or both at the terminal (omega) carbon atom of G and/or at the adjacent

carbon atom (omega-minus-one). Particularly preferred in this regard are Formula XIII-to-XXVIII compounds wherein G is defined as $-(CH_2)_b-X$ wherein b is zero, one, 2, 3, or 4, and X is isobutyl, tert-butyl, 3,3-difluorobutyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, or 3,3,4,4,4-pentafluorobutyl. Among these last preferences, the optimum combination of biological response specificity and potency is usually obtained when the combination of $-(CH_2)_b-$ and $-X$ results in a chain of 5 carbon atoms, excluding methyl branching. Thus, is is preferred that b is one when X is 3,3-difluorobutyl, 4,4,4-trifluorobutyl, or 3,3,4,4,4-pentafluorobutyl, 2 when X is isobutyl, and 3 when X is tert-butyl. When G is substituted alkyl, it is preferred that the 1-position be mono- or di-substituted with one ore two alkyl groups containing from one to 4 carbon atoms, inclusive. Especially preferred are Formula XIII-to-XXVIII compounds wherein G is substituted at the 1-position with methyl and/or ethyl, e.g.

$$-CH(CH_3)-(CH_2)_c-CH_3,\ -CH(CH_2H_5)-(CH_2)_c-CH_3,$$

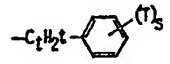
$$-C(CH_3)_2-(CH_2)_c-CH_3,\ -C(C_2H_5)_2-(CH_2)_c-CH_3,$$

or

$$-C(CH_3)(C_2H_5)-(CH_2)_c-CH_3,$$

wherein c is 2, 3, or 4.

When G represents



as defined above, it is preferred for compounds with optimum combination of biological properties that C_tH_{2t} be a valence bond, i.e., t is zero, or alkylene of one to 4 carbon atoms, inclusive, i.e., $-(CH_2)_d-$ wherein d is one, 2, 3, or 4, with or without a fluoro or alkyl substituent on the carbon adjacent to the hydroxy-substituted carbon (C-15 in PGE_1), e.g., $-CHF-(CH_2)_e-$, $-CH(CH_3)-(CH_2)_e-$, or

$$-C(CH_3)_2-(CH_2)_e-,$$

wherein e is zero, one, 2, or 3. Further, it is preferred that the phenyl ring when present and substituted, be substituted at least at the para position.

Another advantage of the novel compounds of this invention, especially the preferred compounds defined hereinabove, compared with the known prostaglandins, is that these novel compounds are administered effectively orally, sublingually, intravaginally, buccally, or rectally, in addition to usual intravenous, intramuscular, or subcutaneous injection or infusion methods indicated above for the uses of the known prostaglandins. These qualities are advantageous because they facilitate maintaining uniform levels of these compounds in the body with fewer, shorter, or smaller doses, and make possible self-administration by the patient.

The PGE, PGF_α, PGF_β, PGA, and PGB type oxa-phenylene compounds encompassed by Formulas XIII to XXVIII including the special classes of compounds described above, are used for the purposes described above in the free acid form, in ester form, or in pharmacologically acceptable salt form. When the ester form is used, the ester is any of those within the above definition of R_1. However, it is preferred that the ester be alkyl of one to four carbon atoms, inclusive. Of those alkyl, methyl and ethyl are especially preferred for optimum absorption of the compound by the body or experimental animal system.

Pharmacologically acceptable salts of these Formula XIII-to-XXVIII compounds useful for the purposes described above are those with pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations.

Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminium, zinc, and iron, are within the scope of this invention.

Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines. Examples of suitable amines are methylamine, dimethylamine, trimethylamine, ethylamine, dibutylamine, triisopropylamine, N-methylhexylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, and like aliphatic, cycloaliphatic, and araliphatic amines containing up to and including about 18 carbon atoms, as well as heterocyclic

amines, e.g., piperidine, morpholine, pyrrolidine, piperazine, and lower-alkyl derivatives thereof, e.g., 1-methylpiperidine, 4-ethylmorpholine, 1-isopropylpyrrolidine, 2-methylpyrrolidine, 1,4-dimethylpiperazine and 2-methylpiperidine, as well as amines containing water-solubilizing or hydrophilic groups, e.g., mono-, di-, and triethanolamine, ethyldiethanolamine, N-butylethanolamine, 2-amino-1-butanol, 2-amino-2-ethyl-1,3-propanediol, 2 - amino - 2 - methyl - 1 - propanol, tris-(hydroxymethyl)-aminomethane, N-phenylethanolamine, N - (*p* - tert - amylphenyl)diethanolamine, galactamine, N-methylglucamine, N-methylglucosamine, ephedrine, phenylephrine, epinephrine, and procaine.

Examples of suitable pharmacologically acceptable quaternary ammonium cations are tetramethylammonium, tetraethylammonium, benzyltrimethylammonium and phenyltriethylammonium.

The PGE, PGF_α, PGF_β, PGA, and PGB type oxa-phenylene compounds encompassed by Formulas XIII to XXVIII including the special classes of compounds described above, are also used for the purposes described above in free hydroxy form or in the form wherein the hydroxy radicals are transformed to lower alkanoate radicals, e.g., —OH to $—OCOCH_3$. Examples of lower alkanoate groups are acetoxy, propionyloxy, butyryloxy, valeryloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, and branched chain alkanoyloxy isomers of those radicals. Especially preferred among these alkanoates for the above described purposes are the acetoxy compounds. These free hydroxy and alkanoyloxy compounds are used as free acids, as esters, and in salt form all as described above.

As discussed above, the compounds of Formulas XIII to XXVIII are administered in various ways for various purposes; e.g., intravenously, intramuscularly, subcutaneously, orally, intravaginally, rectally, buccally, sub-lingually, topically, and in the form of sterile implants for prolonged action.

For intravenous injection or infusion, sterile aqueous isotonic solutions are preferred. For that purpose, it is preferred because of increased water solubility that R_1 in the Formula XIII-to-XXVIII compound be hydrogen or a pharmacologically acceptable cation. For subcutaneous or intramuscular injection, sterile solutions or suspensions of the acid, salt, or ester form in aqueous or non-aqueous media are used. Tablets, capsules, and liquid preparations such as syrups, elixirs, and simple solutions, with the usual pharmaceutical carriers are used for oral sublingual administration. For rectal or vaginal administration, suppositories prepared as known in the art as used. For tissue implants, a sterile tablet or silicone rubber capsule or other object containing or impregnated with the substance is used.

Accordingly the present invention provides a therapeutic composition comprising as the active ingredient one of the compounds of the invention together with a pharmaceutically acceptable carrier.

The PGE, PGF_α, PGF_β, PGA, and PGB type oxa-phenylene compounds encompassed by Formulas XIII to XXVIII are produced by the reactions and procedures described and exemplified hereinafter.

The various PGF_α-type and PGF_β-type oxa-phenylene compounds encompassed by Formulas XVII to XX are prepared by carbonyl reduction of the corresponding PGE type compounds encompassed by Formulas XIII to XVI. For example, carbonyl reduction of 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 gives a mixture of 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ and 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\beta}$.

These ring carbonyl reductions are carried out by methods known in the art for ring carbonyl reductions of known prostanoic acid derivatives. See, for example, Bergstrom et al., Arkiv Kemi 19, 563 (1963), Acta Chem. Scand. 16, 969 (1962), and British Specification No. 1,097,533. Any reducing agent is used which does not react with carbon-carbon double or triple bonds or ester or acid groups. Preferred reagents are lithium(tri-tert-butoxy)aluminium hydride, the metal borohydrides, especially sodium, potassium and zinc borohydrides, the metal trialkoxyborohydrides, e.g., sodium trimethoxyborohydride. The mixtures of alpha and beta hydroxy reduction products are separated into the individual alpha and beta isomers by methods known in the art for the separation of analogous pairs of known isomeric prostanoic acid derivatives. See, for example, Bergstrom et al., cited above, Granstrom et al., J. Biol. Chem. 240, 457 (1965), and Gréen et al., J. Lipid Research 5, 117 (1964). Especially preferred as separation methods are partition chromatographic procedures, both normal and reversed phase, preparative thin layer chromatography, and countercurrent distribution procedures.

The various PGA-type oxa-phenylene compounds encompassed by Formulas XXI to XXIV are prepared by acidic dehydration of the corresponding PGE type com-

pounds encompassed by Formulas XIII to XVI. For example, acidic dehydration of 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 gives 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1.

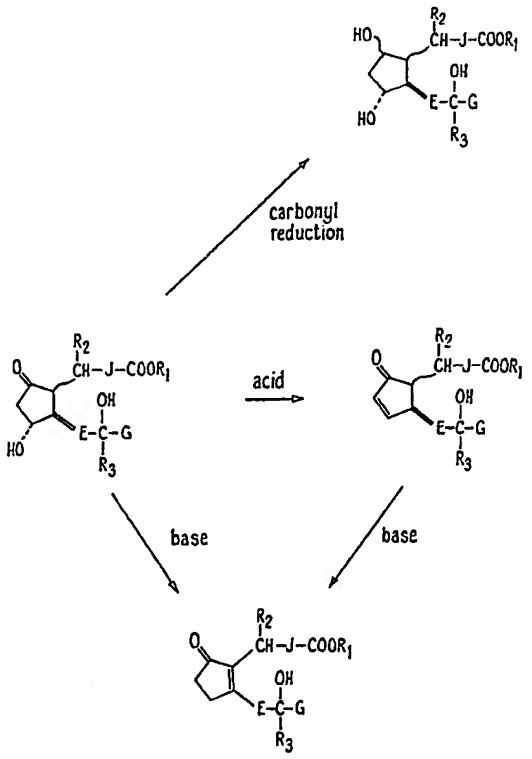
These acidic dehydrations are carried out by methods known in the art for acidic dehydrations of known prostanoic acid derivatives. See, for example, Pike et al., Proc. Nobel Symposium II, Stockholm (1966), Interscience Publishers, New York, pp. 162—163 (1967); and British Specification 1,097,533. Alkanoic acids of 2 to 6 carbon atoms, inclusive, especially acetic acid, are preferred acids for this acidic dehydration. Dilute aqueous solutions of mineral acids, e.g., hydrochloric acid, especially in the presence of a solubilizing diluent, e.g., tetrahydrofuran, are also useful as reagents for this acidic dehydration, although these reagents may cause partial hydrolysis of an ester reactant.

The various PGB-type oxa-phenylene compounds encompassed by Formulas XXV to XXVIII are prepared by basic dehydration of the corresponding PGE type compounds encompassed by Formulas XIII to XVI or by contacting the corresponding PGA type compounds encompassed by Formulas XXI to XXIV with base. For example, both 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 and 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1 give 3-oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor PGB_1 on treatment with base.

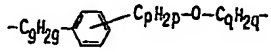
These basic dehydrations and double bond migrations are carried out by methods known in the art for similar reactions of known prostanoic acid derivatives. See, for example, Bergstrom et al., J. Biol. Chem. 238, 3555 (1963). The base is any whose aqueous solution has pH greater than 10. Preferred bases are the alkali metal hydroxides. A mixture of water and sufficient of a water-miscible alkanol to give a homogeneous reaction mixture is suitable as a reaction medium. The PGE-type or PGA-type compound is maintained in such a reaction medium until no further PGB-type compound is formed, as shown by the characteristic ultraviolet light absorption near 278 mμ for the PGB type compound.

The various transformations of PGE-type oxa-phenylene compounds of Formulas XIII to XVI to the corresponding PGF_α, PGF_β, PGA, and PGB type oxa-phenylene compounds are shown in Chart A, wherein R_1, R_2, R_3, G, and ~ are as

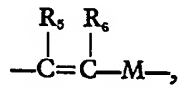
CHART A



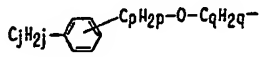
defined above, wherein E is $—CH_2CHR_4—$ or *trans*—$CH=CR_4—$, when J is



or E is *trans* CH=CR$_4$ when J is *cis* or *trans*



or —C≡C—M—, wherein M is



and wherein C_gH_{2g}, C_jH_{2j}, C_pH_{2p}, C_qH_{2q}, R_5, and R_6 are as defined above.

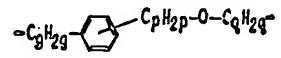
The various dihydro-PGE$_1$, dihydro-PGF$_{1\alpha}$, dihydro-PGF$_{1\beta}$, dihydro-PGA$_1$ and dihydro-PGB$_1$ type oxa-phenylene compounds encompassed by Formulas XVI, XX, XXIV, and XXVIII are prepared by carbon-carbon double bond reduction of the corresponding PGE, PGF$_\alpha$, PGF$_\beta$, PGA, and PGB type compound containing a *trans* double bond in the hydroxy-containing side chain. A *cis* or *trans* double bond or triple bond can also be present in the carboxy-terminated side chain of the unsaturated reactant, and will be reduced at the same time to —CH_2CH_2—. For example, 13,14 - dihydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE$_1$ is produced by reduction of 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE$_1$, 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE$_2$, or 5,6 - dehydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6- trinor- PGE$_2$.

These reductions are preferably carried out by reacting the unsaturated PGE, PGF$_\alpha$, PGF$_\beta$, PGA, or PGB type oxa-phenylene compound with diimide, following the general procedure described by van Tamelen et al., J. Am. Chem. Soc. 83, 3725 (1961). See also Fieser et al., "Topics in Organic Chemistry," Reinhold Publishing Corp., New York, pp. 432—434 (1963) and references cited therein. The unsaturated acid or ester reactant is mixed with a salt of azodiformic acid, preferably an alkali metal salt such as the disodium or dipotassium salt, in the presence of an inert diluent, preferably a lower alkanol such as methanol or ethanol, and preferably in the absence of substantial amounts of water. At least one molecular equivalent of the azodiformic acid salt is used for each multiple bond equivalent of the unsaturated reactant. The resulting suspension is then stirred, preferably with exclusion of oxygen, and the mixture is made acid, advantageously with a carboxylic acid such as acetic acid. When a reactant wherein R_1 is hydrogen is used, the carboxylic acid reactant also serves to acidify an equivalent amount of the azodiformic acid salt. A reaction temperature in the range of 10° to 40°C. is usually suitable. Within that temperature range, the reaction is usually complete within less than 24 hours. The desired dihydro product is then isolated by conventional methods, for example, evaporation of the diluent, followed by separation from inorganic materials by solvent extraction.

In the case of the oxa-phenylene unsaturated PGE, PGF$_\alpha$, and PGF$_\beta$ type reactants, the reductions to the corresponding dihydro-PGE$_1$, dihydro-PGF$_{1\alpha}$, and dihydro-PGF$_{1\beta}$ type oxa-phenylene compounds are also carried out by catalytic hydrogenation. For that purpose, palladium catalysts, especially on a carbon carrier, are preferred. It is also preferred that the hydrogenation be carried out in the presence of an inert liquid diluent, for example, methanol, ethanol, dioxane, and ethyl acetate, Hydrogenation pressures ranging from atmospheric to 50 p.s.i., and hydrogenation temperatures ranging from 10° to 100°C. are preferred. The resulting dihydro product is isolated from the hydrogenation reaction mixture by conventional methods, for example, removal of the catalyst by filtration or centrifugation, followed by evaporation of the solvent.

Diimide reductions and catalytic hydrogenations to produce the various novel Formula XVI, XX, XXIV, and XXVIII dihydro compounds of this invention from the corresponding PGE, PGF, PGF$_\beta$, PGA, and PGB type oxa-phenylene compounds

of the PG_1, PG_2 *trans*-5,6-dehydro-PG_1, and 5,6-dehydro-PG_2 series are shown in Chart B. G, J, R_1, R_2, R_3, R_4, and ~ are as defined above, and L is



wherein C_gH_{2g}, C_pH_{2p}, and C_qH_{2q} are as defined above.

The oxa-phenylene compounds of the PGE_2, $PGF_{2\beta}$, PGA_2, and PGB_2 type wherein the carbon-carbon double bond in the carboxy-terminated side chain is in *cis* configuration are prepared by reduction of the corresponding acetylenic oxa-phenylene compounds, i.e., those with a carbon-carbon triple bond in place of said carbon-carbon double bond. For that purpose, there are used any of the known reducing agents which reduce an acetylenic linkage to a *cis*-ethylenic linkage. Especially preferred for that purpose are diimide, or hydrogen and a catalyst, for example, palladium (5%) on barium sulfate, especially in the presence of pyridine. See Fieser et al., "Reagents for Organic Synthesis," pp. 566—567, John Wiley & Sons, Inc., New York, N.Y. (1967). These reductions are shown in Chart C, wherein G, M, R_1, R_2, R_3, R_4, and ~ are as defined above. These oxa-phenylene *cis* compounds of the PGE_2, $PGF_{2\alpha}$, $PGF_{2\beta}$, PGA_2, and PGB_2 type are also prepared as described hereinafter.

The oxa-phenylene PGE-type compounds of Formulas XIII

CHART B

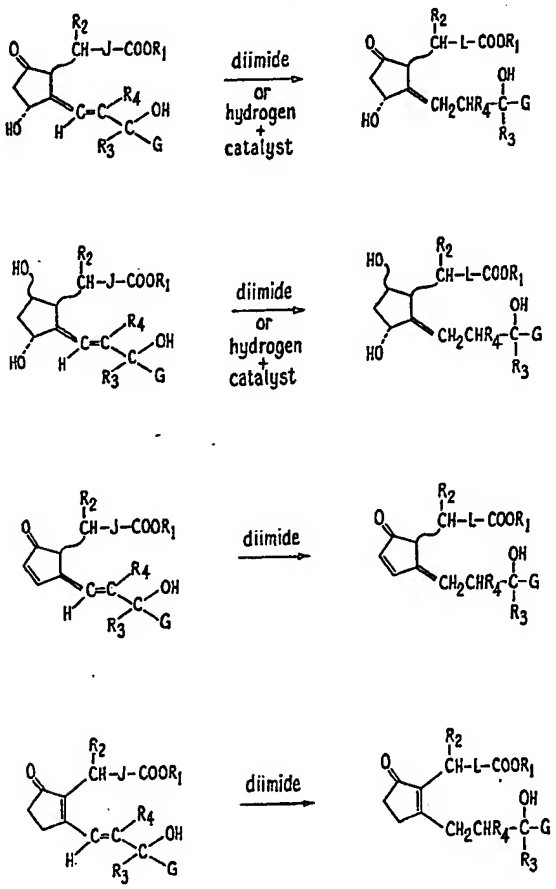
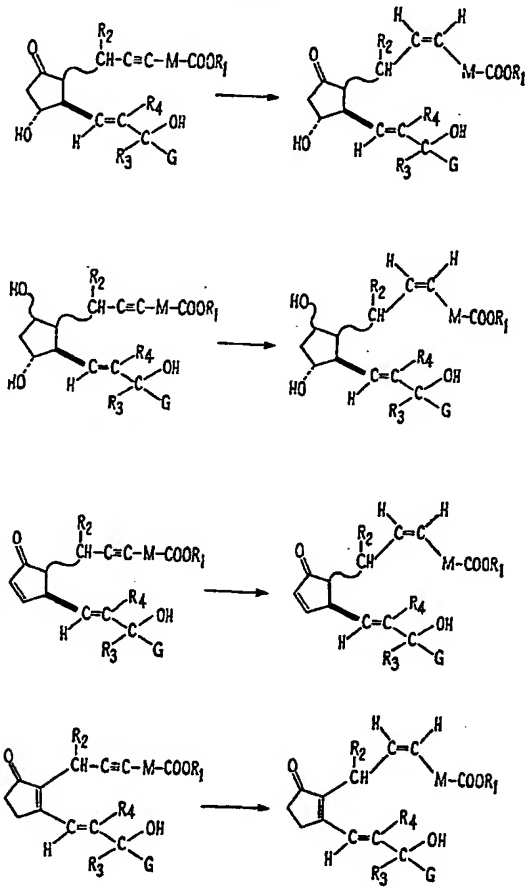


CHART C



to XVI except wherein R_1 is hydrogen, and the oxa-phenylene PGA-type compounds of Formulas XXI to XXIV except wherein R_1 is hydrogen are prepared by the series of reactions shown in Chart D, wherein G, J, R_2, R_3, and R_4 are as defined above; G′ is the same as G except that T is replaced by T′, wherein T′ is the same as T above except that R_9 is not hydrogen; R_{10} is the same as the above definition of R_1 except that R_{10} does not include hydrogen; R_{11} and R_{12} are alkyl of one to 4 carbon atoms, inclusive; R_{13} is alkyl of one to 5 carbon atoms, inclusive; and ~ indicates attachment of $-CHR_2-J-COOR_{10}$ to the cyclopentane ring in alpha or beta configuration, and *exo* or *endo* configuration with respect to the radical attached to the cyclopropane ring.

The oxa-phenylene PGE_1-type compounds of Formula XIII, the oxa-phenylene 5,6-dehydro-PGE_2 type compounds of Formula XV, the oxa-phenylene PGA_1-type compounds of Formula XXI and the oxa-phenylene 5,6-dehydro-PGA_2 type compounds of Formula XXIII are also prepared by the series of reactions shown in Chart E, wherein G, G′, R_2, R_3, R_4, R_{10}, and R_{13} are as defined above; Z is L or $-C\equiv C-M-$ wherein L and M are as defined above; and ~ indicates attachment of $-CHR_2-Z-COOR_{10}$ to the cyclopentane ring in alpha or beta configuration and *exo* or *endo* configuration with respect to the radical attached to the cyclopropane ring.

CHART D

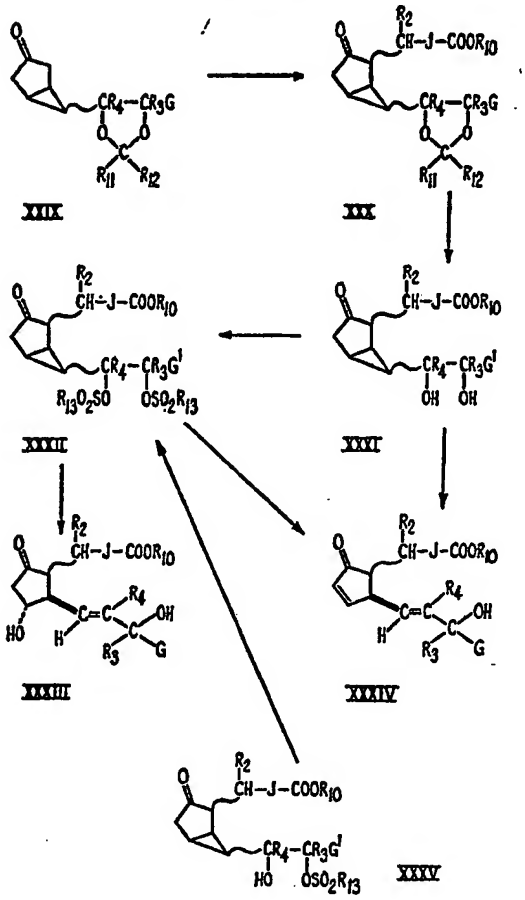
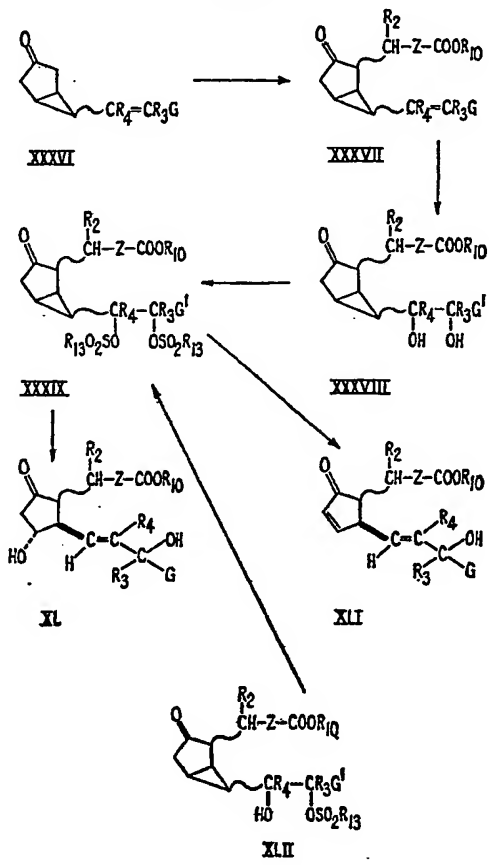


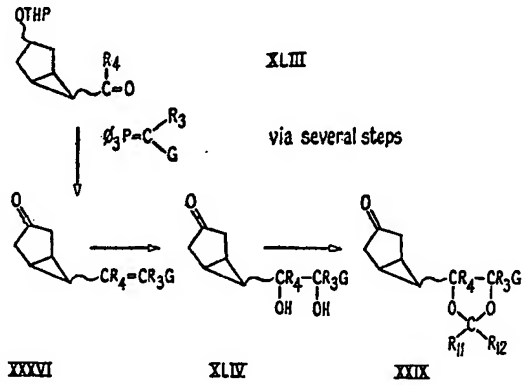
CHART E



It should be observed regarding the series of reactions shown in Charts D and E, that the reactions starting with glycol XXXI in Chart D are similar to the reactions starting with glycol XXXVIII in Chart E. The only differences here are the definitions of the divalent radicals (Chart D) and Z (Chart E). J includes saturated *cis* and *trans* ethylenic, and acetylenic divalent radicals. Z is limited to the saturated and acetylenic divalent radicals encompassed by J. In other words, final oxa-phenylene PGE-type compounds of Formula XXXIII (Chart D) encompass compounds of Formulas XIII to XVI. Final oxa-phenylene PGA-type compounds of Formula XXXIV (Chart D) encompass compounds of Formulas XXI to XXIV. On the other hand, final oxa-phenylene PGE-type compounds of Formula XL (Chart E) encompass only compounds of Formulas XIII and XV, and final oxa-phenylene PGA-type compounds of Formula XLI (Chart E) encompass only compounds of Formulas XXI and XXIII.

As will subsequently appear, an acetylenic intermediate of Formulas XXX, XXXI, or XXXVIII is transformed by stepwise reduction to the corresponding *cis* or *trans* ethylenic intermediates of Formulas XXX or XXXI; and an acetylenic intermediate of Formulas XXX, XXXI, or XXXVIII or a *cis* or *trans* ethylenic intermediate of Formulas XXX or XXXI is transformed by reduction to the corresponding saturated intermediate of Formulas XXX, XXXI, or XXXVIII.

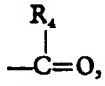
The initial bicyclo-ketone reactant of Formula XXXVI in Chart E is also used as an initial reactant to produce the initial bicyclo-ketone cyclic ketal reactant of Formula XXIX in Chart D. The following reactions will produce cyclic ketal XXIX, wherein THP is 2-tetrahydropyranyl, and ϕ is phenyl:



The bicyclo-ketone reactant of Formula XXXVI exists in four isomeric forms, *exo* and *endo* with respect to the attachment of the $—CR_4=CR_3G$ radical, and *cis* and *trans* with respect to the double bond in that same radical. Each of those isomers separately or various mixtures thereof are used as reactants according to this invention to produce substantially the same final oxa-phenylene PGE or PGA type product mixture.

The process for preparing either the *exo* or *endo* configuration of the Formula-XXXVI bicyclo-ketone is known to the art. See Belgian Patent No. 702,477; reprinted in Farmdoc Complete Specifications, Book 714, No. 30,905, page 313, March 12, 1968. See West Germany Offenlegungsschrift No. 1,937,912; reprinted in Farmdoc Complete Specifications, Book No. 14, No. 6869 R, Week R_5, March 18, 1970.

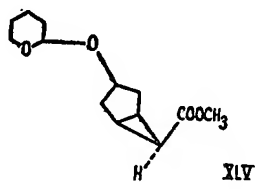
In said Belgian Patent No. 702,477, a reaction sequence capable of forming *exo* ketone XXXVI is as follows: The hydroxy of 3-cyclopentenol is protected, for example, with a tetrahydropyranyl group. Then a diazoacetic acid ester is added to the double bond to give an *exo-endo* mixture of a bicyclo[3.1.0]hexane substituted at 3 with the protected hydroxy and at 6 with an esterified carboxyl. The *exo-endo* mixture is treated with a base to isomerize the endo isomer in the mixture to more of the exo isomer. Next, the carboxylate ester group at 6 is transformed to an aldehyde group or ketone group, —CHO or



wherein R_4 is as defined above. Then, said aldehyde group or said keto group is transformed by the Wittig reaction, in this case to a radical of the formula $—CR_4=CR_3G$ which is in *exo* configuration relative to the bicyclo ring structure. Next, the protective group is removed to regenerate the 3-hydroxy which is then oxidized, for example, by the Jones reagent, i.e., chromic acid (see J. Chem. Soc. 39 (1946)), to give said *exo* ketone XXXVI.

Separation of the *cis-exo* and *trans-exo* isomers of XXXVI is described in said Belgian Patent No. 702,477. However, as mentioned above, that separation is usually not necessary since the *cis-trans* mixture is useful as a reactant in the next process step.

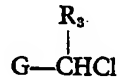
The process described in said Belgian Patent No. 702,477 for producing the *ex.* form of bicyclo-ketone XXXVI uses, as an intermediate, the *exo* form of a bicyclo-[3.1.0]hexane substituted at 3 with a protected hydroxy, e.g., 2-tetrahydropyranyloxy, and at 6 with an esterified carboxyl. When the corresponding *endo* compound is substituted for that *exo* intermediate, the process in said Offenlegungsschrift No. 1,937,912 leads to the *endo* form of bicycloketone XXXVI. That *endo* compound to be used has the formula:



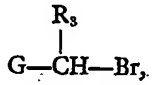
Compound XLV is prepared by reacting *endo*-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester with diborane in a mixture of tetrahydrofuran and diethyl ether, a reaction generally known in the art, to give *endo*-bicyclo[3.1.0]hexane-3-ol-6-carboxylic acid methyl ester which is then reacted with dihydropyran in the presence of a catalytic amount of $POCl_3$ to give the desired compound. This is then used as described in said Offenlegungsschrift no. 1,937,912 to produce the *endo* form of bicyclo-ketone XXXVI.

As for exo XXXVI, the above process produces a mixture of *endo-cis* and *endo-trans* compounds. These are separated as described for the separation of *exo-cis* and *exo-trans* XXXVI, but this separation is usually not necessary since, as mentioned above, the *cis-trans* mixture is useful as a reactant in the next process step.

In the processes of said Belgian patent and said Offenlegungsschrift, certain organic halides, e.g., chlorides and bromides, are necessary to prepare the Wittig reagents used to generate the generic radical $—CR_4=CR_3G$ of bicyclo-ketone XXXVI. These organic chlorides and bromides

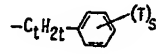


and



are known in the art or can be prepared by methods known in the art.

To illustrate the availability of these organic chlorides consider the above-described oxa-phenylene PGE-type compounds of Formulas XIII to XVI, wherein R_3 is hydrogen (H) and G is either (a) hydrogen, (b) alkyl of one to 10 carbon atoms, inclusive, substituted with zero, one, 2, or 3 fluoro, (c) alkyl of 2 to 10 carbon atoms, inclusive, substituted with 4 or 5 fluoro on the omega and omega-minus-one carbon atoms, or (d)



wherein C_tH_{2t} represents a valence bond or alkylene of one to 10 carbon atoms, inclusive, substituted with zero, one, or 2 fluoro, with one to 7 carbon atoms, inclusive, between $—CR_3OH—$ and the ring; wherein T is alkyl of one to 4 carbon atoms, inclusive, fluoro, chloro, trifluoromethyl, or $—OR_9$, wherein R_9 is hydrogen, alkyl of one to 4 carbon atoms, inclusive, or tetrahydropyranyl, and s is zero, one, 2, or 3, with the proviso that not more than two T are other than alkyl, and when two or three T's are present or substituents they may be the same or different.

For types H-(a) and H-(b) above, i.e. wherein R_3 is hydrogen and G is either (a) hydrogen or (b) alkyl of one to 10 carbon atoms, saturated with 0—3 fluorine atoms, there are available the monohalo hydrocarbons, e.g. bromo- (or chloro-)methane, -ethane, -propane, -pentane, -octane, and -decane; and the monohalofluorohydrocarbons, e.g.

CH_2FCH_2Br, CHF_2CH_2Cl, CF_3CH_2Br, $F(CH_2)_3Br$, $CH_3CF_2CH_2Cl$,

$CF_3(CH_2)_2Br$, $F(CH_2)_4Cl$, $CH_3CF_2CH_2CH_2Cl$, $C_4H_9CFH\,CH_2Br$,

$CF_3(CH_2)_3Cl$, $CF_3(CH_2)_2Br$, $CH_2F(CH_2)_4Cl$,

$C_2H_5CF_2(CH_2)_2Cl$, $CF_3(CH_2)_4Cl$, $CH_3(CH_2)_4CF_2(CH_2)_2CH_2Cl$,

and

$CH_3(CH_2)_3CF_2(CH_2)_3CH_2Cl$,

as described in "Aliphatic Fluorine Compounds", A. M. Lovelace et al, Am. Chem. Soc. Monograph Series, 1958, Reinhold Publ. Corp. Those halides not available are prepared by methods known in the art by reacting the corresponding primary alcohol $G—CH_2OH$ with PCl_3, PBr_3, or any of the other halogenating agents useful for this purpose. Available alcohols include $CH_2CH(CF_3)CH_2OH$, $(CH_3)_2CHCH_2CH_2OH$, $(CH_3)_3CCH_2OH$, $CF_3CH(CH_3)CH_2CH_2OH$, for example. For those halides of the formula $G—CH_2—Hal$ wherein Hal is chloro or bromo, G is $—(CH_2)_h—X$, h being zero, one, 2, 3, or 4, and X being isobutyl, tert-butyl, 3,3-difluorobutyl, 4,4-difluorobutyl, or 4,4,4-trifluorobutyl, the intermediate alcohols are prepared as follows.

In the case of X being isobutyl or tert-butyl, known alcohols are converted to bromides, thence to nitriles with sodium cyanide, thence to the corresponding carboxylic acids by hydrolysis, and thence to the corresponding primary alcohols by reduction, e.g.

with lithium aluminium hydride, thus extending the carbon chain one carbon atom at a time until all primary alcohols are prepared.

In the case of X being 3,3-difluorobutyl, the necessary alcohols are prepared from keto carboxylic acids of the formula, $CH_3—CO—(CH_2)_r—COOH$, wherein r is 2, 3, 4, 5, or 6. All of those acids are known. The methyl esters are prepared and reacted with sulfur tetrafluoride to produce the corresponding $CH_3—CF_2—(CH_2)_r—COOCH_3$ compounds, which are then reduced with lithium aluminium hydride to

$$CH_3—CF_2—(CH_2)_r—CH_2OH.$$

These alcohols are then transformed to the bromide or chloride by reaction with PBr_3 or PCl_3.

In the case of X being 4,4-difluorobutyl, the initial reactants are the known dicarboxylic acids, $HOOC—(CH_2)_f—COOH$, wherein f is 3, 4, 5, 6, or 7. These dicarboxylic acids are esterified to $CH_3OOC—(CH_2)_f—COOCH_3$ and then half-saponified, for example with barium hydroxide, to give $HOOC—(CH_2)_f—COOCH_3$. The free carboxyl group is transformed first to the acid chloride with thionyl chloride and then to an aldehyde by the Rosenmund reduction. Reaction of the aldehyde with sulfur tetrafluoride then gives $CHF_2—(CH_2)_f—COOCH_3$ which by successive treatment with lithium aluminium hydride and PBr_3 or PCl_3 gives the necessary bromides or chlorides, $CHF_2—(CH_2)_f—CH_2Br$ or $CHF_2—(CH_2)_f—CH_2Cl$. Those formulas can be rewritten as $CHF_2CH_2CH_2CH_2(CH_2)_d—CH_2Br$ or $CHF_2CH_2CH_2CH_2(CH_2)_d—CH_2Cl$.

In the case of X being 4,4,4-trifluorobutyl, aldehydes of the formula

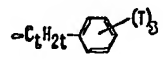
$$CH_3OOC—(CH_2)_f—CHO$$

are prepared as described above. Reduction of the aldehyde with sodium borohydride gives the alcohol $CH_3OOC—(CH_2)_f—CH_2OH$. Reaction with PBr_3 or PCl_3 then gives $CH_3OOC—(CH_2)_f—CH_2—X$. Saponification of that ester gives the carboxylic acid which by reacting with sulfur tetrafluoride gives the necessary $CF_3—(CH_2)_f—CH_2—Br$ or $CF_3—(CH_2)_f—CH_2—Cl$.

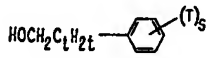
For the above reactions of SF_4, see U.S. 3,211,723 and J. Org. Chem. 27, 3164 (1962).

For type H-(c) above, i.e. where R_3 is hydrogen and G is alkyl of 2 to 1 Dearlon atoms substituted with fluoro on the ω and ω-1 carbon atoms, available monohalofluorocarbons are used, e.g. $C_2F_5CH_2Br$ or $C_2F_5CH_2Cl$, or such halides are prepared from available alcohols, e.g. $HCF_2CF_2(CH_2)_3OH$. For those halides of the formula $G—CH_2—Hal$ wherein G is $—(CH_2)_h—X$, X being 3,3,4,4,4-pentafluorobutyl the known alcohol of the formula $CF_3CF_2CH_2OH$ is reacted with PBr_3 or PCl_3 to give $CF_3CF_2CH_2Br$ or $CF_3CF_2CH_2Cl$. Reaction of those halides with sodium cyanide, hydrolysis of the resulting nitrile, reduction of the resulting acid with lithium aluminium hydride, and reaction of the resulting primary alcohol with PBr_3 or PCl_3 gives the first member of this series, $CF_3CF_2CH_2CH_2Br$ or $CF_3CF_2CH_2CH_2Cl$. Repetition of this series of reactions produces, one by one, the remaining necessary primary pentafluoro bromides or chlorides.

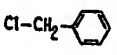
For type H—(d) above, i.e. where R_3 is hydrogen and G is



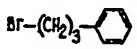
the halides necessary to prepare those compounds, if not readily available, are advantageously prepared by reacting the corresponding primary alcohol,



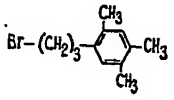
with PCl_3, PBr_3, HBr, or any of the other halogenating agents known in the art to be useful for this purpose. Some of the readily available halides are shown in Table I wherein s, T, and t of the formula for the intermediate halides are as defined above, and Hal is chloro, bromo, or iodo. Thus, compound No. 1 of Table 1 is represented by the formula wherein S and t are zero, and Hal is chloro, i.e.



namely α-chlorotoluene or benzyl chloride; compound No. 8 of Table I is represented by the formula wherein s is zero, t is 2, and Hal is bromo, i.e.



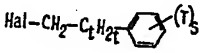
namely 1-bromo-3-phenylpropane or 3-bromopropylbenzene; and compound No. 63 of Table I represented by the formula wherein s is 3, T is methyl in the 2-, 4- and 5-positions with respect to the C_tH_{2t} substitution, t is 2, and Hal is bromo, i.e.,



namely 1-(3-bromopropyl)-2,4,5-trimethylbenzene.

TABLE I

Intermediate Halides represented by the formula



No.	s	T	t	Hal
1	0	—	0	Cl
2	0	—	0	Br
3	0	—	0	I
4	0	—	1	Cl
5	0	—	1	Br
6	0	—	1	I
7	0	—	2	Cl
8	0	—	2	Br
9	0	—	2	I
10	0	—	3	Cl
11	0	—	3*	Cl
12	0	—	3	Br
13	0	—	4	Cl
14	1	2-CH_3	0	Cl
15	1	2-C_2H_5	0	Cl
16	1	4-C_2H_5	0	Cl
17	1	2-CF_3	0	Cl
18	1	4-OCH_3	0	Cl

*—branched 

TABLE I (Continued)

No.	s	T	t	Hal
19	1	3-CH_3	0	Br
20	1	4-CH_3	0	Br
21	1	C—C_5H_{11}	0	Br
22	1	4-Cl	0	Br
23	1	2-CF_3	0	Br
24	1	3-CF_3	0	Br
25	1	4-CH_3	0	I
26	1	4-F	1	Cl
27	1	3-Cl	1	Br
28	1	4-Cl	1	Br
29	1	4-F	1	Br
30	1	2-Cl	2	Br
31	1	3-Cl	2	Br
32	1	4-Cl	2	Br
33	1	4-F	3*	Br
34	1	2-Cl	4	Br
35	2	2-CH_3, 4-CH_3	0	Cl
36	2	2-CH_3, 5-CH_3	0	Cl
37	2	2-CH_3, 6-CH_3	0	Cl
38	2	3-CH_2, 4-CH_3	0	Cl
39	2	2-CH_3, 4-Cl	0	Cl
40	2	2-CH_3, 5-CH_3	0	Br
41	2	2-CH_3, 6-CH_3	0	Br
42	2	3-CH_3, 5-t-butyl	0	Br

*—branched —CH(Et)—

TABLE I (Continued)

No.	s	T	t	Hal
43	2	3-CH_3, 4-Cl	0	Br
44	2	2-CH_3, 3-Br	0	Br
45	2	3-OCH_3, 4-OCH_3	0	Cl
46	2	3-OCH_3, 5-OCH_3	0	Cl
47	2	3-OCH_3, 5-OCH_3	0	Br
48	2	2-CH_3, 4-CH_3	1	Cl
49	2	2-CH_3, 4-CH_3	1	Br
50	2	3-CH_3, 4-CH_3	1	Br
51	2	3-OCH_3, 4-OCH_3	1	Br
52	2	3-OCH_3, 5-OCH_3	1	Br
53	2	3-OCH_3, 4-OCH_3	1	I
54	2	3-OCH_3, 4-OCH_3	2	Br
55	2	3-OCH_3, 5-OCH_3	2	Br
56	2	3-OCH_3, 5-OCH_3	4	Br
57	3	2-CH_3, 4-CH_3, 5-CH_3	0	Cl
58	3	2-CH_3, 4-CH_3, 6-CH_3	0	Cl
59	3	4-CH_3, 2-OCH_3, 5-OCH_3	0	Cl
60	3	2-CH_3, 3-CH_3, 6-CH_3	0	Br
61	3	2-CH_3, 4-CH_3, 6-CH_3	0	Br

TABLE I (Continued)

No.	s	T	t	Hal
62	3	2-CH_3, 3-OCH_3, 6-OCH_3	0	Br
63	3	2-CH_3, 4-CH_3, 5-CH_3	2	Br

Next, considering the intermediate halides for producing oxa-phenylene PGE-type compounds of Formulas XIII to XVI, wherein R_3 is alkyl of one to 4 carbon atoms, inclusive (A), and G is either of the four types (a), (b), (c), or (d) above, these organic chlorides and bromides,

$$G—\underset{\displaystyle R_3}{\underset{|}{CH}}—Hal,$$

are known to the art or can be prepared by methods known in the art.

For types A-(a) and A-(b) above, i.e. where R_3 is alkyl and G is either (a) hydrogen or (b) alkyl of one to 10 carbon atoms substituted with 0—3 fluorine atoms, there are available such monohalofluorohydrocarbons as $CHF_2CHClCH_3$, $CF_3CHBrCH_3$, $CF_3CH_2CHBrCH_3$, $CH_3CF_2CHClCH_3$, $CF_3CHClC_2H_5$, and $C_2H_5CF_2CHClCH_3$, for example. Those not readily available are prepared from the corresponding secondary alcohol

$$G—\underset{\displaystyle R_3}{\underset{|}{CH}}—COH,$$

wherein R_3 is as defined above, with PCl_3, PBr_3, or any of the other halogenating agents known in the art to be useful for this purpose. Such alcohols include, for example,

$CH_2FCH(OH)CH_2F$, $CF_3(CH_2)_2CH(OH)CH_3$, $CF_3CH(OH)(CH_2)CH_3$,

$CF_3CH(OH)(CH_2)_3CH_3$, $CF_3CH(OH)C(CH_3)_3$,

and

$CF_3CH(OH)(CH_2)_5CH_3$.

In the case of X being isobutyl or tert-butyl, lower molecular weight primary alcohols are transformed to the corresponding longer-chain carboxylic acids and thence to the corresponding secondary alcohols by preparing the intermediate ketones,

$$G—\underset{\displaystyle R_3}{\underset{|}{C}}=O$$

by known procedures, for example $G—COCl+(R_3)_2Cd$, thereafter reducing the ketone to the secondary alcohol with sodium borohydride.

In the case of X being 3,3-difluorobutyl, the procedure described above is applicable to converting $CH_3—CF_2—(CH_2)_2—COOCH_3$ described above to

$$CH_3—CF_2—(CH_2)_2—\underset{\displaystyle R_3}{\underset{|}{CH}}OH.$$

These alcohols are then transformed to the bromide or chloride by reaction with PBr_3 or PCl_3.

In the case of X being 4,4-difluorobutyl, the corresponding secondary alcohols are prepared as described above, using intermediates prepared for the primary alcohols of this type above.

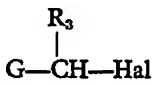
In the case of X being 4,4,4-trifluorobutyl, corresponding secondary alcohols are prepared by transforming $CH_3OOC—(CH_2)_f—CHO$ to $CH_3OOC—(CH_2)_f—C(R_3)O$ by known methods and then proceeding with that ketone as described above for the aldehyde under the type H-(b) intermediates.

For the type A-(c) halides, i.e. where R_3 is alkyl and G is alkyl of 2 to 10 carbon atoms substituted with 4—5 fluoro on the ω and ω-1 carbon atoms, available secondary alcohols are transformed by the usual reactions with PCl_3 or PBr_3, using for example,

$CF_3CF_2CH(OH)CH_3$, $CF_3CF_2CH(OH)CH_2CH_3$,

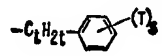
$CF_3CF_2CH(OH)(CH_2)_3CH_3$, and $CF_3CF_2CH(OH)C(CH_3)_3$.

For those halides of the formula

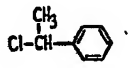


wherein G is $—(CH_2)_a—X$, X being 3,3,4,4,4-pentafluorobutyl, the appropriate carboxylic acid intermediate prepared as described above under type H-(c) is transformed to an alkyl ketone, thence by reduction to the secondary alcohol, and finally by bromination or chlorination, e.g. with PBr_3 or PCl_3, to the desired secondary halide.

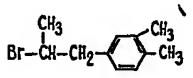
For type A-(d) halides, i.e. where R_3 is alkyl and G is



some of the readily available halides are shown in Table II. Thus, compound No. 1 of Table II is represented by the formula wherein s=0, R_3=methyl, t=0, and Hal=Cl, i.e.



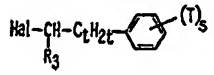
namely (1-chloroethyl)benzene; and compound No. 13 of Table II is represented by the formula wherein s=2, T=methyl, R_3=methyl, t=1, and Hal=Br, i.e.



namely 4 - (2 - bromopropyl) - *o* - xylene or 1 - (2 - bromopropyl)3,4 - dimethylbenzene

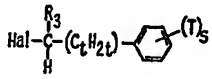
TABLE II

Intermediate Halides represented by the Formula

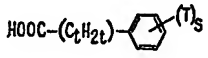


No.	s	T	R_3	t	Hal
1	0	—	CH_3	0	Cl
2	0	—	C_2H_5	0	Cl
3	0	—	C_2H_5	0	Br
4	0	—	CH_3	0	I
5	0	—	CH_3	1	Cl
6	0	—	n-C_3H_7	1	Cl
7	0	—	CH_3	1	Br
8	0	—	C_2H_5	2	Cl
9	1	4-C_2H_5	CH_3	0	Cl
10	1	4-F	CH_3	0	Cl
11	1	4-Cl	C_2H_5	0	Br
12	1	4-F	C_2H_5	0	Br
13	2	3-CH_3, 4-CH_3	CH_3	1	Br
14	2	3-OCH_3, 4-OCH_3	CH_3	1	Br
15	2	2-OCH_3, 6-OCH_3	CH_3	1	Br

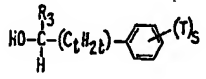
Other intermediate halides of the general formula



may be obtained from the secondary alcohols as discussed above. The secondary alcohols, wherein R_3 is alkyl, are prepared by transforming the —COOH of the corresponding carboxylic acid,

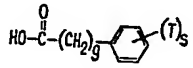


to a ketone by known procedures, e.g. by way of the acyl chloride and a dialkylcadmium. Reduction of the ketone with sodium borohydride then yields the secondary alcohol,

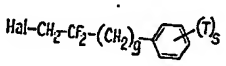


Hydroxyl groups on the aromatic ring are suitably protected during these reactions by first forming the corresponding tetrahydropyranyl ethers with dihydropyran; the hydroxyl groups are restored by mild acid hydrolysis as is well known in the art.

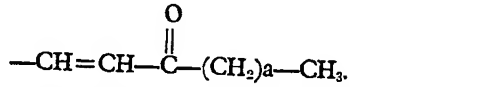
In the case of C_tH_{2t} substituted with one or 2 fluoro atoms, there are a number of routes to the intermediate halides. The corresponding alcohols, for example β-fluorophenethyl alcohol, β-fluoro-α-methyl-phenethyl alcohol, and β-fluoro-α,β-dimethyl-phenethyl alcohol are reacted with PCl_3, PBr or HBr to form the halide. Alternatively, the carboxylic acid having one less carbon atom in the chain than the desired intermediate halide, i.e.



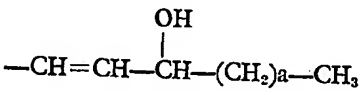
where g=t−1, is converted by a series of known methods to the 2,2-difluorohalide. Thus, the free carboxyl group is transformed first to the acid chloride with thionyl chloride and thence by way of the nitrile to the α-keto-acid. The carboxyl group is reduced to the alcohol with diborane and then converted to the α-keto halide. Finally, by reaction of the keto group with sulfur tetrafluoride, there is obtained



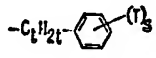
As mentioned above, Formula XIII-to-XXVIII compounds with an alpha-fluoro substituent in a straight chain 3-to-7-carbon G, i.e., G being —CHF—(CH_2)a—CH_3 wherein a is one, 2, 3, 4, or 5, represent preferred embodiments among the novel oxaphenylene compounds of this invention. Among those, for example, is 3-oxa-16-fluoro-3-7-inter-*m*-phenylene-4,5,6-trinor-PGE_1. The Formula-XXXVI bicyclo-ketones necessary to produce those mono-fluoro compounds are advantageously prepared by reacting either of the above-mentioned bicyclo-aldehydes, *exo* or *endo*, with a Wittig reagent prepared from CH_3—(CH_2)a—CO—CH_2—Br and triphenylphosphine. The aldehyde group is thereby transformed to



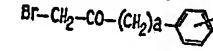
The resulting unsaturated ketone is reduced to the corresponding



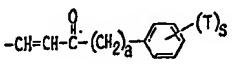
compound. The —OH in that group is replaced with fluoro by known methods, for example, directly by reaction with 2-chloro-1,1,2-trifluorotriethylamine or indirectly, for example, by transforming the hydroxy to tosyloxy or mesyloxy, and reacting the resulting compound with anhydrous potassium fluoride in diethylene glycol. Similarly, the oxaphenylene PG-type compounds wherein G is



having an alpha-fluoro substituent on the carbon adjacent to the hydroxy-substituted carbon (C-15 in PGE_1) represent preferred embodiments of this invention. In preparing the Formula-XXXVI bicycloketone intermediates, there is used a Wittig reagent prepared from

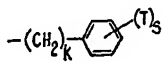


and triphenylphosphine. Following the steps above, the resulting unsaturated ketone containing the moiety



is reduced to the corresponding secondary alcohol. The —OH in that group is replaced by fluoro by known methods.

Another preference mentioned above is that the 1-position of G in the Formula XIII-to-XXXVIII compounds be mono- or di-substituted with alkyl of one to 4 carbon atoms, particularly methyl or ethyl. In the steps of the synthesis shown in Charts D and E, G is then G'''—$CR_{21}R_{22}$— wherein R_{21} and R_{22} are methyl or ethyl and G''' is preferably alkyl of 2 to 6 carbon atoms or

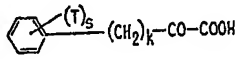


wherein k is zero one, 2, or 3. Thus, in preparing the Formula-XXXVI intermediate olefin, a Wittig reagent is prepared from a halo compound of the general formula G'''—$CR_{21}R_{22}$—CR_3H—Hal wherein Hal is chloro or bromo. These compounds are known in the art or can be prepared by methods known in the art, including those methods described above.

For example, when G''' is $CH_3(CH_2)_3$—, R_3 and R_{21} are hydrogen, and R_{22} is methyl, there is employed 1-bromo (or -chloro)-2-methylhexane. If the halo compound is not available, the corresponding carboxylic acid is transformed to the alcohol and thence to the halide. Thus, 2,2-diethylvaleric acid yields 1-bromo-2,2-diethylpentane, wherein G''' is $CH_3(CH_2)_2$—, R_3 is hydrogen, and R_{21} and R_{22} are ethyl.

2-Ethylhexanoic acid yields 3-chloromethylheptane, wherein G''' is $CH_3(CH_2)_3$—, R_3 and R_{21} are hydrogen, and R_{22} is ethyl. 2-Ethyl-2-methylhexanoic acid yield 3-bromomethyl-3-methylheptane, wherein G''' is $CH_3(CH_2)_3$—, R_3 is hydrogen, R_{21} is methyl, and R_{22} is ethyl. 2-Phenylpropionic acid yields 1-bromo-2-phenylpropane, wherein G''' is phenyl, R_3 and R_{21} are hydrogen, and R_{22} is methyl. 2-Methyl-2-phenylbutyric acid yields 1-bromo-2-methyl-2-phenylbutane, wherein G''' is phenyl, R_3 is hydrogen, R_{21} is methyl, and R_{22} is ethyl. 2 - Methyl - 4 - (2,4,5 - trimethoxyphenyl)-butyric acid yields 1 - chloro - 2 - methyl - 4 - (2,4,5 - trimethoxyphenyl) - butane, wherein G''' is (2,4,5-trimethoxyphenyl)ethyl, R_3 and R_{21} are hydrogen, and R_{22} is methyl.

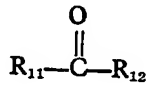
Mono-alkyl substituted alkanoic acids useful for preparing the above halo intermediates are prepared by alkylation of an α-keto acid, G'''—CO—COOH, e.g.



(prepared via the acid chloride and thence the nitrile) by means of a Grignard reagent, $R_{22}MgHal$ for example.

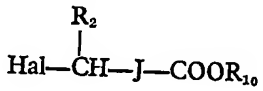
The transformation of bicyclo-ketone-olefin XXXVI to glycol XLIV is carried out by reacting olefin XXXVI with a hydroxylation reagent. Hydroxylation reagents and procedures for this purpose are known in the art. See, for example, Gunstone, Advances in Organic Chemistry, Vol. 1, pp. 103—147, Interscience Publishers, New York, N.Y. (1960). Various isomeric glycols are obtained depending on such factors as whether olefin XXXVI is *cis* or *trans* and *endo* or *exo*, and whether a *cis* or a *trans* hydroxylation reagent is used. These various glycol mixtures are separated into individual isomers by silica gel chromatography. However, this separation is usually not necessary, since each isomeric threo glycol is useful as an intermediate according to this invention and the processes outlined in Chart D to produce final products of Formulas XXXIII and XXXIV, and then, according to Charts A, B, and C to produce the other final products of this invention. Thus, the various isomeric glycol mixtures encompassed by Formula XLIV produced from the various isomeric olefins encompassed by Formula XXXVI are all useful for these same purposes.

The transformation of glycol XLIV to the cyclic ketal of Formula XXIX (Chart D) is carried out by reacting said glycol with a dialkyl ketone of the formula

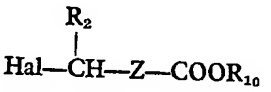


wherein R_{11} and R_{12} are alkyl of one to 4 carbon atoms, inclusive, in the presence of an acid catalyst, for example potassium bisulfate or 70% aqueous perchloric acid. A large excess of the ketone and the absence of water is desirable for this reaction. Examples of suitable dialkyl ketones are acetone, methyl ethyl ketone, diethyl ketone, and methyl propyl ketone. Acetone is preferred as a reactant in this process.

Referring again to Chart D, cyclic ketal XXIX is transformed to cyclic ketal XXX by alkylating with an alkylation agent of the formula



wherein R_2, R_{10}, and J are as defined above, and Hal is chlorine, bromine, or iodine. Similarly, referring to Chart E, olefin XXXVI is transformed to olefin XXXVII by alkylating with an alkylation agent of the formula

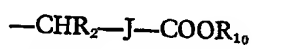


wherein R_2, R_{10}, Z, and Hal are as defined above.

Any of the alkylation procedures known in the art to be useful for alkylating cyclic ketones with alkyl halides and haloalkanoic esters are used for the transformations of XXIX to XXX, and of XXXVI to XXXVII. See, for example, the above-mentioned Belgian patent No. 702,477 for procedures useful here and used there to carry out similar alkylations, e.g. employing the bicyclo enamines.

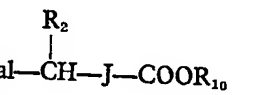
For these alkylations, it is preferred that Hal be bromo or iodo. Any of the usual alkylation bases, e.g., alkali metal alkoxides, alkali metal amides, and alkali metal hydrides, are useful for this alkylation. Alkli metal alkoxides are preferred, especially tert-alkoxides. Sodium and potassium are preferred alkali metals. Especially preferred is potassium tert-butoxide. Preferred diluents for this alkylation are tetrahydrofuran and 1,2-dimethoxyethane. Otherwise, procedures for producing and isolating the desired Formula-XXX and -XXXVII compounds are within the skill of the art.

These alkylation procedures produce mixtures of alpha and beta alkylation products, i.e., a mixture of Formula-XXX products wherein part has the

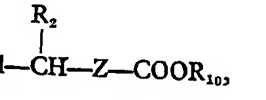


radical in both alpha and beta configurations. When about one equivalent of base per equivalent of Formula-XXIX or -XXXVI ketone is used, the alpha configuration usually predominates. Use of an excess of base and longer reaction times usually result in production of larger amounts of beta products. These alpha-beta isomer mixtures are separated at this stage or at any subsequent stage in the multi-step processes shown in Charts D and E. Silica gel chromatography is preferred for this separation.

The necessary alkylating agents for the above-described alkylations, e.g. compounds of the formulas

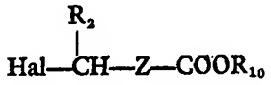


and

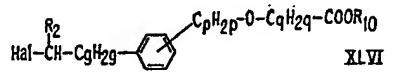


are prepared by methods known in the art. There are four groups of compounds encompassed by these two genera of alkylating agents.

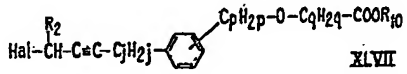
Alkylating agents of the formula



include compounds of the formulas:

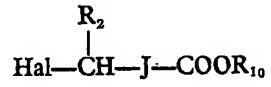


XLVI

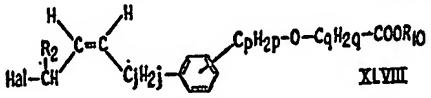


XLVII

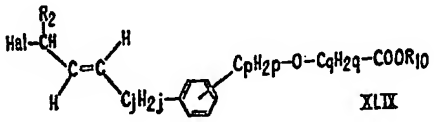
Alkylating agents of the formula



include the above-listed compounds of Formulas XLVI and XLVII, and also compounds of the following formulas:

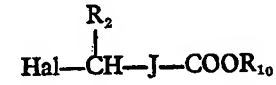


XLVIII

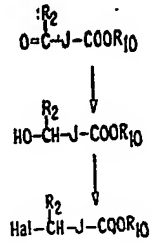


XLIX

These alkylating agents of Formulas XLVI to XLIX are accessible to those of ordinary skill in the art. In one route, the



compounds are obtained from aldehyde or ketone reactants by a series of transformations as follows:



L

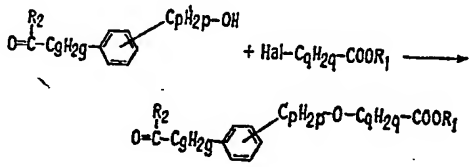
LI

LII

For example, methyl *m*-formylphenoxyacetate on reduction with sodium borohydride yields methyl *m*-(hydroxymethyl)phenoxyacetate, which in turn is transformed to the Formula-LII compound, methyl *m*-(chloromethyl)phenoxyacetate, with thionyl chloride.

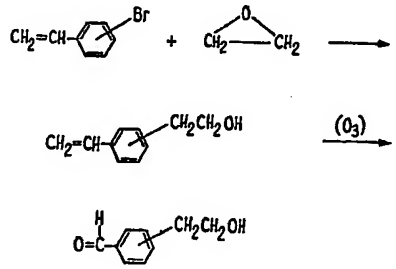
Those Formula-L or Formula-LI reactants which are not commercially available

are advantageously prepared by adaptation of the Willimson ether syntheses, e.g. employing a hydroxy reactant and a halo-substituted acid or ester. Thus, the reaction



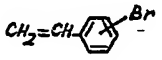
wherein Hal is chloro, bromo, or iodo, preferably iodo, proceeds in the presence of a strong base, for example sodium hydride when R_1 is a carbon-containing group, and lithium diisopropyl amide when R_1 is hydrogen. Within the definitions of C_gH_{2g}, C_pH_{2p}, and C_qH_{2q}, suitable reactants are readily available or are prepared by methods known to those skilled in the art.

Thus, when R_2 is hydrogen, and considering the variations of C_gH_{2g} and C_pH_{2p}, the aldehyde reactants include (*o*, *m*, or *p*)-hydroxybenzaldehyde, (*o*, *m*, or *p*-hydroxyphenyl)acetaldehyde, (*o* or *p*)-hydroxyhydrocinnamaldehyde, 4-(*o* or *p*-hydroxyphenyl)-butyraldehyde, and *o*-[(2-hydroxyethyl)]benzaldehyde. Other aldehyde reactants are also accessible by methods known to those skilled in the art. For example, [*o*, *m*, or *p*-(2-hydroxyethyl)]benzaldehydes are obtained from (*o*, *m*, or *p*)-bromostyrene by the series of reactions:

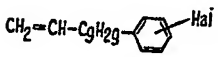


The reaction with ethylene oxide is carried out on a Grignard reagent prepared from the bromostyrene and magnesium. Substituted ethylene oxides are used to obtain substituted C_pH_{2p} chains, e.g. propylene oxide, 1,2-exoxy-2-methylpropane, 1,2-epoxybutane, and 1,2-epoxy-2,3-dimethylbutane. Instead of using ozone to form the aldehyde, hydroxylation and oxidation with osmium tetroxide and periodic acid are optional (see J. Org. Chem. 21, 478, 1956).

Compounds with C_gH_{2g} chains are obtained by replacing



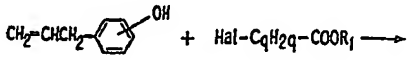
with

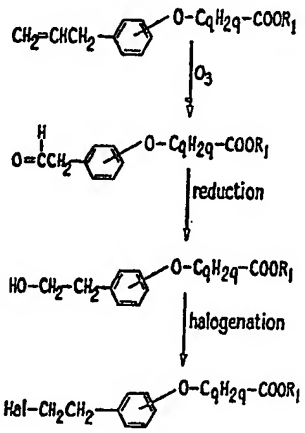


e.g. 1-allyl-4-bromobenzene, 1-allyl-2-chlorobenzene, and 4-(*o*, *m*, or *p*-chlorophenyl)-1-butene. Compounds with C_pH_{2p} chains are obtained by replacing ethylene oxide with suitable alkylating agents, e.g. trimethylene oxide, 1,3-epoxybutane, and 1,3-epoxy-3-methylbutane or suitable reaction steps.

Other variations of the above reactions and reactants will be apparent to those skilled in the art. Thus, an alkene-substituted phenol is condensed with a halo-sub-

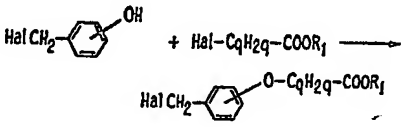
stituted acid or ester and thereafter transformed as an aldehyde to the halo alkylating agent within the scope of Formula LII by the following steps:





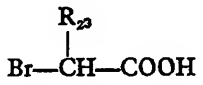
Available for this series of reactions are (*o*, *m*, or *p*)-vinylphenol, *p*-allylphenol, and 4-(*o*, *m*, or *p*-hydroxyphenyl)-1-butene.

Alternatively, a haloalkylphenyl is condensed with a halo-substituted acid or ester by the reaction:



Available are *p*-(2-bromoethyl)phenol, and *p*-(3-bromobutyl)phenol.

Considering the halo-substituted acid or ester reactants in the above ether syntheses and the variations of C_qH_{2q}, there are a wide variety of reactants available, which will lead to the desired Formula-LII alkylating agent. For example:



wherein R_{23} is hydrogen or alkyl of one to 5 carbon atoms, inclusive;

$Br—(CH_2)_2—COOH$, $Br—C(CH_3)_2—COOH$, $Br—C(C_2H_5)_2—COOH$,

$BrC(CH_3)(C_2H_5)—COOH$, $Br—CH(CH_3)—CH_2—COOH$,

$Br—(CH_2)_3—COOCH_3$ $Cl—CH(C_2H_5)—CH_2—COOCH_3$,

$Cl—CH(n—C_3H_7)—CH_2—COOCH_3$, $Br—CH(CH_3)—(CH_2)_2—COOC_2H_5$,

$Br—CH(CH_3)—CH_2—CH(CH_3)—COOC_2H_5$,

$Br—CH(CH_3)—CH(CH_3)—CH_2—COOC_2H_5$,

$Br—C(CH_3)_2—CH_2—CH(CH_3)—COOC_2H_5$,

$Cl—CH(n—C_4H_9)—CH_2—COOC_2H_5$, $Cl—C(CH_3)_2—CH_2—COOC_2H_5$,

$Br—CH(n—C_2H_7)—(CH_2)_2—COOH$,

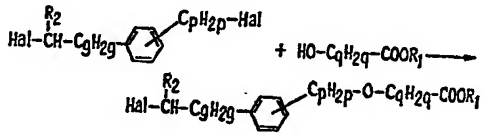
and

$Cl—CH(C_2H_5)—(CH_2)_2—COOH$

are available. The preferred iodo reactants are obtained by methods known to those skilled in the art.

When C_qH_{2q} has two alkyl groups attached to the ω or ω-1 carbon atom of the halo-substituted acid or ester reactants, it is preferred that halo be replaced with mesyloxy or tosyloxy prior to the ether synthesis, and, that relatively mild bases and reaction conditions be used, for example, potassium tert-butoxide in dimethyl sulfoxide.

In another route to the Formula-LII alkylating agents, the Williamson ether syntheses employs hydroxy-esters or acids of the formula $HO—C_qH_{2q}—COOR_1$ for condensation with halo-substituted reactants as follows:



For example, α,α'-dibromo-*o*-xylene is contacted with ethyl glycolate in the presence of sodium hydride to yield ethyl [o-(bromomethyl)benzyloxy]acetate.

Typical halo reactants which are useful for this reaction are α-bromo-(*o*, *m*, or *p*)-chlorotoluene, 1-bromo-(2 or 3)-(2-bromoethyl)benzene, 1-(3-bromopropyl)-(1 or 2)-chlorobenzene, and 1-(4-bromobutyl)-1-chlorobenzene.

When C_pH_{2p} has two alkyl groups attached to the carbon atom to which Hal is attached, it is preferred that this Hal be replaced with mesyloxy or tosyloxy prior to the ether synthesis and that relatively mild bases and reaction conditions be used.

Considering the hydroxy acid or ester reactants, there are available a wide range of suitable compounds within the scope of $HO—C_qH_{2q}—COOR_1$ which will lead to the desired Formula-LII alkylating agent. For example:

$HOCH(CH_3)—COOCH_3$, $HOC(CH_3)_2—COOH$, $HOCH(C_2H_5)—COOH$,

$HOC(CH_3)(C_2H_5)—COOH$, $HO(CH_2)_2—COOC_2H_5$, $HOCH(CH_3)—CH_2—COOH$,

$HOCH(n—C_3H_7)—COOH$, $HOC(n—C_3H_7)(CH_3)—COOH$,

$HOCH(C_2H_5)—CH_2—COOH$, $HOCH(CH_3)—(CH_2)_2—COOH$,

$HOCH(n—C_4H_9)—COOH$, $HOC(n—C_4H_9)(CH_3)—COOH$,

$HOCH(n—C_3H_7)—CH_2—COOCH_3$, $HOCH(C_2H_5)—(CH_2)_2—COOH$,

$HOCH(n—C_5H_{11})—COOH$, $HOCH(n—C_4H_9)—CH_2—COOH$,

$HOCH(n—C_3H_7)—(CH_2)_2—COOH$

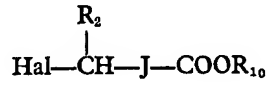
are available.

When a Formula-LII alkylating agent is desired in which there are two alkyl substituents on both carbon atoms attached to the oxa —O—, it is preferred that, if the halo-acid route be used, the halo atom on the acid be chloro and that freshly precipated wet magnesium hydroxide in an inert solvent suspension be used as the base; and if the hydroxy-acid route be used, the $—C_pH_{2p}—Hal$ group is preferably $—C_pH_{2p}—Cl$. If the hydroxy-acid route is used with $—C_pH_{2p}—I$, silver oxide is used as the base.

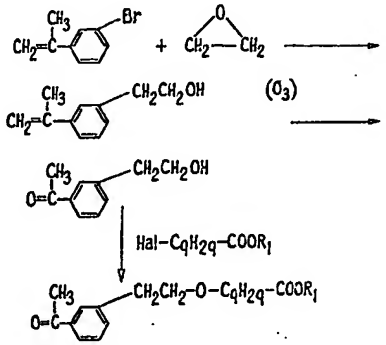
The alkylating agents of Formulas XLVI to XLIX are esters. Any of the above acid forms are readily converted to esters. Variations in R_{10} within the definition of R_{10} herein, are readily made by methods known in the art. The ester moiety is chosen according to the desired type of final oxa-phenylene PG-type product.

Formula-L aldehyde reactants which lead to the Formula-LII alkylating agents are also obtained by reaction of halo-substituted aldehydes with hydroxy acids or ester reactants. Thus, there are employed o-(bromoethyl)benzaldehyde, p-chlorohydratropaldehyde, and the like.

When R_2 is alkyl, the Formula-LII

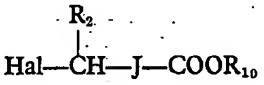


alkylating agents are prepared from the corresponding reactants wherein R_2 is methyl, ethyl, propyl, or butyl, or their isomers. For example *m*-bromo-α-methylstyrene reacts as follows:

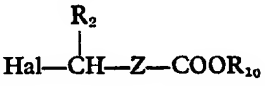


Typical halo-substituted ketones available for this purpose include (2′, 3′, or 4′)-(bromo, chloro, or iodo)-acetophenone, (3′ or 4′)-bromopropiophenone, (3′ or 4′)-chlorobutyrophenone, and 4′-(bromo or chloro)-valerophenone. Other reactants leading to the R_2 (alkyl)-substituted Formula-LII alkylating agents are accessible to those skilled in the art.

Although the above methods are generally useful for preparing alkylating agents within the scope of formulas

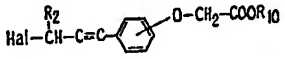


and

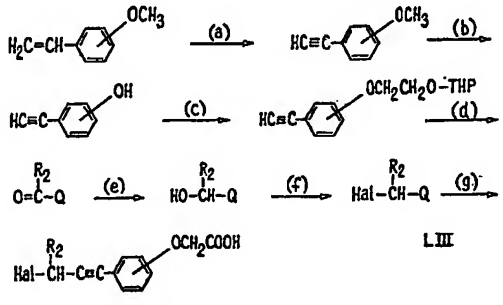


above, there are preferred methods for preparing the Formula-XLVII compounds containing the $-C\equiv C-C_jH_{2j}-$ moiety.

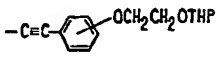
Considering the compounds of the formula



there is employed as starting material (*o*, *m*, or *p*-)vinylanisole in the following series of transformations:

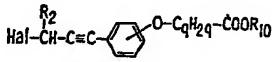


Herein, THP represents 2-tetrahydropyranyl and Q represents

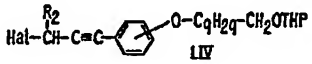


The reagents and conditions for bringing about these transformations are known to those skilled in the art. Thus, in step a, reacting first with bromine and then with sodium amide in liquid ammonia yields the acetylenic derivative (see J. Am. Chem. Soc. 56, 2064, 1934). Step b utilizes boron tribromide for example. Step c proceeds either with ethylene chlorohydrin and a strong base, e.g., NaOH or KOH, followed by dihydropyran in the presence of an acid catalyst, or with the tetrahydropyranyl ether of the chlorohydrin and a strong base. Step d utilizes R_2COCl in the presence of a strong base, e.g., sodium amide, phenyllithium, or sodium triphenylmethane. Alternatively, if R_2 is desirably hydrogen, paraformaldehyde is employed and step e omitted (see J. Am. Chem. Soc. 92, 6314 (1970). The reaction in step e is done with a metal hydride, e.g., sodium borohydride. In step f thionyl chloride yields the Formula-LIII chloro compounds. Finally, in step g the THP moiety is selectively removed by mild hydrolysis in acid medium and the terminal $—CH_2OH$ radical is oxidized to —COOH, e.g. with the Jones reagent. The alkylating agent is converted by known means to an ester, as defined by R_{10}, to yield the desired compounds.

Considering the compounds of the formula



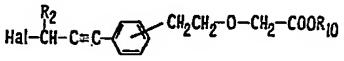
the above series of transformations are used, except that in step c $ClCH_2CH_2OH$ is replaced by $Cl—C_qH_{2q}—CH_2OH$. There are obtained in step f compounds of the formula



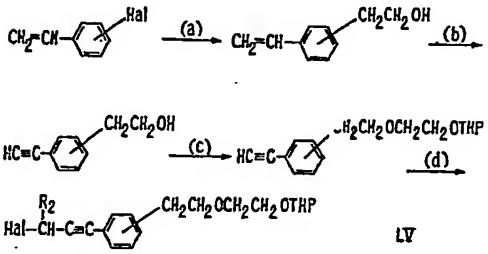
LIV

wherein C_qH_{2q}, Hal, R_2 and THP are as defined above. Thereafter these Formula-LIV compounds are transformed as in step g above to the desired compounds.

Considering the compounds of the formula



there are employed as starting materials the ar-halostyrenes. These are transformed by the following steps:



LV

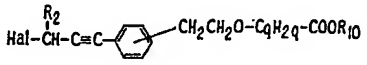
Thereafter, these Formula-LV compounds are transformed as in step g above to the desired compounds. In step a, the halo compounds are converted to a Grignard reagent with magnesium and thence reacted with ethylene oxide. In step b, the hydroxy group is converted to —OTHP with dihydropyran, the acetylenic moiety is formed as in step

a leading to the Formula-LIII compounds above, and the THP moiety removed by mild acid hydrolysis. In step c, the chain is extended by reaction with

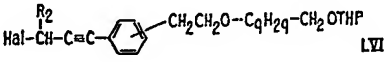
$$Hal—CH_2CH_2OH,$$

preferably the bromo or iodo derivatives, in the presence of strong base, e.g., phenyl lithium, sodium triphenylmethane, or sodium hydride. Thereafter, in step d the transformations follow the general scheme of steps d—f leading to the Formula-LIII compound to yield the Formula-LV compounds. Transformation as in step g above yields the desired compounds.

Considering the compounds of the formula



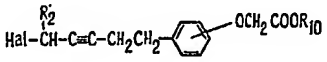
the series of transformations in the paragraph immediately preceeding are used, except that in step c Hal—CH_2CH_2OH is replaced by Hal—C_qH_{2q}—CH_2OH. There are obtained in step d compounds of the formula



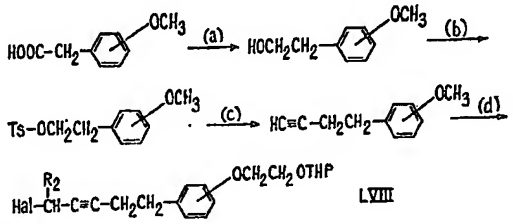
LVI

These Formula-LVI compounds are transformed as in step g above to the desired esters.

Considering the compounds of the formula



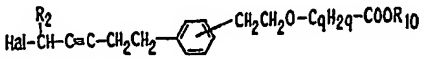
there are employed as starting materials anisoyl aliphatic acids, e.g., anisoyl-acetic acid, in the following steps:



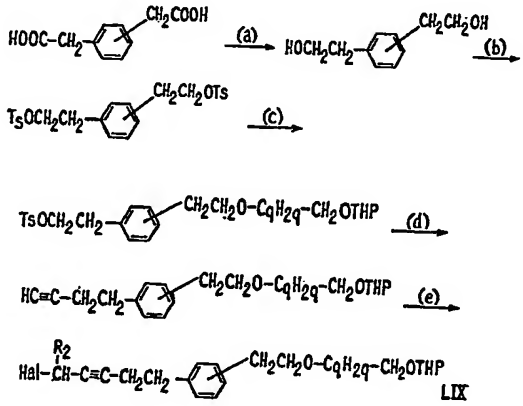
LVIII

In step a, the carboxyl group is reduced with a metal hydride, e.g. lithium aluminium hydride. In step b, where Ts represents the toluenesulfonyl ("tosyl") radical, the reaction is carried out with toluenesulfonyl chloride and pyridine. In step c, the acetylenic radical is introduced with lithium acetylide (see J. Am. Chem. Soc. 80, 6626, 1958) to yield the Formula-LVII intermediates. Subsequent steps in d to form the Formula-LVIII compounds follow from steps b—f for the Formula-LIII compounds above. Finally, the Formula-LVIII compounds are transformed as in step g above to the desired esters.

Considering the compounds of the formula



there are employed as starting materials benzenedialiphatic acids, e.g., benzenediacetic acid, in the following steps:



In step a, the carboxyl groups are reduced with a metal hydride, e.g. lithium aluminium hydride. In step b, reaction with toluenesulfonyl halide yields the bistosyl derivative. In step c one tosyloxy group is replaced by reaction with $HO—C_qH_{2q}—CH_2OTHP$ in the presence of sodium hydride in an inert solvent, e.g. dimethylformamide. In step d, the acetylenic radical is introduced as in forming the Formula-LVII compounds above. Subsequent steps in e to form the Formula-LIX compounds follow from steps b—f for the Formula-LIII compounds above. Finally, the Formula-LIX compounds are transformed as in step g above to the desired esters.

Variations in the above Formula LIII-to-LIX compounds and their corresponding ester alkylating agents as to chain length or branching in the C_gH_{2g}, C_jH_{2j}, C_pH_{2p}, and C_qH_{2q} moieties and as to the identity of R_1 or R_2, within the scope of these terms as herein defined, are available to those skilled in the art making use of the principles disclosed herein.

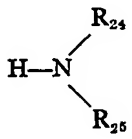
Other modifications which are encompassed within this disclosure include the use of alkylating agents wherein Hal is replaced by hydrocarbonsulfonyl, e.g. tosyl or mesyl (methanesulfonyl) groups. Furthermore, the Formula-LIII, -LIV, -LV, -LVI, -LVIII, and -LIX compounds are alternatively employed as alkylating agents, instead of the corresponding esters, and the alkylated Formula-XXXIX and -XXXVI compounds subsequently converted to the desired Formula-XXX and -XXXVII compounds by mild hydrolysis to remove the THP moiety, oxidation to convert the $—CH_2OH$ moiety to —COOH, and, optionally, esterification to the desired R_1 identity.

The *cis* and *trans* ethylenic alkylating agents of Formulas XLVIII and XLIX above are preferably prepared by *cis* or *trans* reduction of the corresponding Formula-XLVII acetylenic compounds prepared as above, or by *cis* or *trans* reduction of any earlier acetylenic intermediate in which both ends of the acetylenic bond are substituted, i.e., not hydrogen as in the moiety $HC≡C—$. Alternatively, this *cis* or *trans* reduction is carried out on any subsequent acetylenic reaction product leading up to and including the final acetylenic alkylating agent of Formula XLVII.

For these *cis* reductions of the acetylenic bonds, it is advantageous to use hydrogen plus a catalyst which catalyzes hydrogenation of $—C≡C—$ only to *cis* $—CH=CH—$. Such catalysts and procedures are well known to the art. See, for example, Fieser et al., "Reagents for Organic Syntheses", pp. 566—567; John Wiley & Sons, Inc., New York. N.Y. (1967). Palladium (5%) on barium sulfate, especially in the presence of pyridine as a diluent, is a suitable catalyst for this purpose. Alternative reagents useful to transform these acetylenic compounds to *cis*-ethylenic compounds are bis (1,2-dimethylpropyl)borane ("disiamylborane") and diisobutylaluminium hydride.

For *trans* reductions of the acetylenic bond, except for those compounds containing halogen, it is advantageous to use sodium or lithium in liquid ammonia or a liquid alkylamine, e.g., ethylamine. When the radical $HO—CH_2—C≡C—$ is present in the acetylenic compound being reduced, the use of lithium aluminium hydride gives *trans* reduction of the triple bond. Procedures for these *trans* reductions are known in the art. See, for example, Fieser et al., above cited, pp. 577, 592—594, and 603, and J. Am. Chem. Soc. 85, 622 (1963).

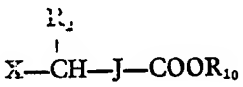
Concerning the alkylation of the cyclopentane ring, another useful alkylation procedure utilizes an intermediate enamine. That enamine is prepared by mixing either the Formula-XXIX ketal or the Formula-XXXVI olefin ketone with a secondary amine of the formula



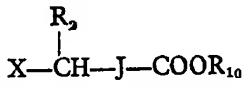
wherein R_{24} and R_{25} are alkyl, cycloalkyl or alkylene linked together through carbon or oxygen to form together with a nitrogen a 5 to 7-membered heterocyclic ring. Examples of suitable amines are diethylamine, dipropylamine, dibutylamine, dihexylamine, dioctylamine, dicyclohexylamine, methylcyclohexylamine, pyrrolidine, 2-methylpyrrolidine, piperidine, 4-methylpiperidine, morpholine, and hexamethylenimine.

The enamine is prepared by heating a mixture of the Formula-XXIX ketal or the Formula-XXXVI olefin ketone with an excess of the amine preferably in the presence of a strong acid catalyst such as an organic sulfonic acid, e.g., *p*-toluenesulfonic acid, or an inorganic acid, e.g., sulfuric acid. It is also advantageous to carry out this reaction in the presence of a water-immiscible diluent, e.g., benzene or soluene, and to remove water by azeotropic distillation as it is formed during the reaction. Then, after water formation ceases, the enamine is isolated by conventional methods.

The enamine is then reacted with a haloester,



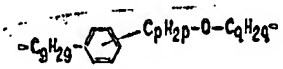
to give the desired Formula-XXX or -XXXVI product. This reaction of the enamine is carried out by the usual procedures. See "Advances in Organic Chemistry," Interscience Publishers, New York, N.Y., Vol. 4, pp. 25—47 (1963) and references cited therein. In addition to halogen, X in



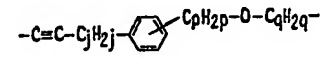
can also be tosylate, and mesylate. It is especially preferred that X be bromine or iodine. Dimethyl sulfoxide is especially useful as a diluent in the reaction of the enamine with the haloester.

Referring again to Chart D, after alkylation as discussed above, cyclic ketal XXX is transformed to glycol XXXI by reacting the cyclic ketal with an acid with pK less than 5. Suitable acids and procedures for hydrolyzing cyclic ketals to glycols are known in the art. Suitable acids are formic acid, hydrochloric acid, and boric acid. Especially preferred as diluents for this reaction are tetrahydrofuran and β-methoxyethanol.

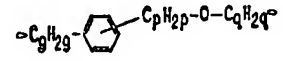
Referring again to Chart E, after alkylation as discussed above, olefin XXXVII is hydroxylated to glycol XXXVIII. As discussed above, the divalent radical —Z— includes the radicals



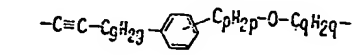
and



wherein C_gH_{2g}, C_jH_{2j}, and C_qH_{2q} are as defined above. When Z is



this hydroxylation of XXXVII is carried out as described above for the hydroxylation of olefin XXXVI to glycol XLIV, i.e., with any of the known reagents and procedures described in Gunstone, above cited. When Z is



some of the reagents and procedures described by Gunstone tend to attack the acetylenic linkage as well as the ethylenic linkage of the Formula-XXXVII olefin. Therefore it is preferred to use a hydroxylation reagent and procedure which attacks the ethylenic linkage preferentially. For this, it is preferred to carry out hydroxylation of these acetylenic Formula-XXXVII olefins with organic peracids, e.g., performic acid, peracetic acid, perbenzoic acid, and *m*-chloroperbenzoic acid, as described by Gunstone, above cited, pp. 124—130.

As discussed above regarding the hydroxylation of unalkylated olefin XXXVI to unalkylated glycol XLIV various isomeric glycols are obtained by hydroxylation of the Formula-XXVII alkylated olefin. The particular Formula-XXXVIII glycol or glycol mixture obtained depends on such factors as whether the olefin XXXVII is *cis or trans* and *endo* or *exo*, and whether a *cis* or a *trans* hydroxylation takes place. However, all of the isomeric Formula-XXXVII erythro and threo glycols and the various glycol mixtures each are useful as an intermediate according to this invention and the processes of Chart E to produce final products of Formulas XL and XLI, and then according to Charts A, B, and C, to produce the other final products of this invention. Therefore, it is usually not necessary to separate individual Formula-XXXVIII glycol isomers before proceeding further in the synthesis, although that separation is accomplished by silica gel chromatography.

It is preferred that glycols XXXI and XXXVIII of Charts D and E, respectively, be free of phenolic hydroxyl substituents before the alkanesulfonation step. If any of the intermediate Formula-XXXI or Formula-XXXVIII compounds have phenolic hydroxyls, these hydroxyls are readily converted to 2-tetrahydropyranyloxy (OTHP) by reaction with dihydropyran, e.g. in the presence of a catalytic amount of $POCl_3$. The —OTHP group is subsequently replaced by OH under mildly acidic conditions.

Referring again to Charts D and E, bis(alkanesulfonic acid) esters XXXII and XXXIX are prepared by reacting glycols XXXI and XXXVIII, respectively, with an alkanesulfonyl chloride or bromide, or with an alkanesulfonic acid anhydride, the alkyl in each containing one to 5 carbon atoms, inclusive. Alkanesulfonyl chlorides are preferred for this reaction. The reaction is carried out in the presence of a base to neutralize the byproduct acid. Especially suitable bases are tertiary amines, e.g., dimethylaniline or pyridine. It is usually sufficient merely to mix the two reactants and the base, and maintain the mixture in the range 0° to 25°C. for several hours. The Formula-XXXII and -XXXIX bis(sulfonic acid) esters are then isolated by procedures known to the art.

Referring now to Chart D, bis(sulfonic acid) esters XXXII are transformed either to oxa-phenylene PGE-type compounds XXXIII, or to oxa-phenylene PGA-type compounds XXXIV. Referring to Chart E, bis(sulfonic acid) esters XXXIX are transformed either to oxa-phenylene PGE-type compounds XL, or to oxa-phenylene PGA-type compounds XLI.

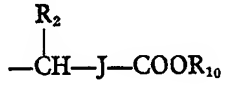
The transformations of XXXII and XXXIX to the PGE-type compounds XXXIII and XL, respectively, are carried out by reacting bis-esters XXXII and XXXIX with water in the range 0° to 60°C. In making the oxa-phenylene PGE_1 compounds, 25°C. is a suitable reaction temperature, the reaction then proceeding to completion in 5 to 20 hours. It is advantageous to have a homogenous reaction mixture. This is accomplished by adding sufficient of a water-soluble organic diluent which does not enter into the reaction. Acetone is a suitable diluent. The desired product is isolated by evaporation of excess water and diluent if one is used. The residue contains a mixture of Formula-XXXIII or Formula-XL isomers which differ in the configuration of the side chain hydroxy, that being either "natural" or "epi", i.e. α or β. These are separated from by-products and from each other by silica gel chromatography. A usual by-product is the mono-sulfonic acid ester of Formula XXXV (Chart D) or Formula XLII (Chart E). These mono-sulfonic acid esters are esterified to the Formula-XXXII or -XXXIX bis(sulfonic acid) esters, respectively, in the same manner described above

for the transformation of glycol XXXI or XXXVIII to bis-ester XXXII or XXXIX and thus are recycled back to additional Formula-XXXIII or -XL final product.

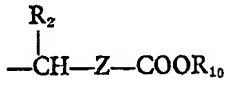
The transformations of XXXII and XXXIX to the PGA type compounds XXXIV and XLI, respectively, are carried out by heating bis-esters XXXII and XXXIX in the range 40° to 100°C. with a combination of water, a base characterized by its water solution having a pH 8 to 12, and sufficient inert water-soluble organic diluent to form a basic and substantially homogenous reaction mixture. A reaction time of one to 10 hours is usually used. Preferred bases are the water-soluble salts of carbonic acid, especially alkali metal bicarbonates, e.g., sodium bicarbonate. A suitable diluent is acetone. The products are isolated and separated as described above for the transformation of bis-esters XXXII and XXXIX to PGE-type products XXXIII and XL. The same mono-sulfonic acid esters XXXV and XLII observed as byproducts in those transformations are also observed during preparation of PGA-type products XXXIV and XLI.

For the transformations of bis(sulfonic acid) esters XXXII and XXXIX to final products XXXIII, XXXIV, XL, and XLI, it is preferred to use the bis-mesyl esters, i.e., compounds XXXII and XXXIX wherein R_{13} is methyl.

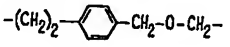
Referring again to Charts D and E, the configuration of the



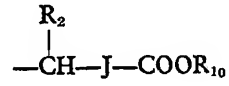
radical in the Formula-XXXII bis-esters or the configuration of the



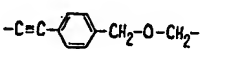
radical in the Formula-XXXIX bis-esters does not change during these transformations of XXXII to XXXIII, XXXIV, and XXXV, and of XXXIX to XL, XLI, and XLII. Therefore, when in Formula XXXII for example, J is



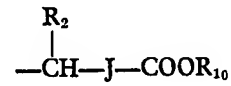
G′ is $—(CH_2)_4—CH_3$, and R_2, R_3 and R_4 are hydrogen, natural- and epi-configuration 3-oxa-4,5-*inter-o*-phenylene-PGE_1 esters (XXXIII) are obtained when



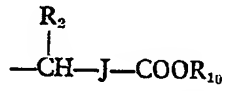
is attached initially (XXXII) in alpha configuration, and natural- and epi-configuration 8-iso-3-oxa-4,5-*inter-o*-phenylene-PGE_1 esters (XXXIII) are obtained when that radical is attached in beta configuration. Similarly, when in Formula XXXII, J is



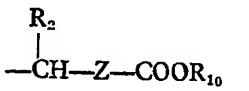
G′ is $—(CH_2)_4—CH_3$, and R_2, R_3, and R_4 are hydrogen, natural- and epi-configuration 5,6-dehydro-3-oxa-4,5-*inter-p*-phenylene-PGE_2 esters are obtained when



is attached initially in alpha configuration, and the corresponding 8-iso compounds are obtained when that radical is attached in beta configuration. The same retention of



configuration occurs when Formula-XXXIV and XXXV compounds are produced, and a similar retention of



configuration occurs when Formula-XL, XLI, and XLII compounds are produced from Formula-XXXIX bis-esters.

The Formula-XXXIII and XL oxa-phenylene PGE-type compounds and the Formula-XXXIV and XLI oxa-phenylene PGA-type compounds shown in Charts D and E are all R_{10} carboxylic acid esters, wherein R_{10} is as defined above. Moreover, when those PGE-type and PGA-type R_{10} esters are used to prepare the other oxa-phenylene prostaglandin-like compounds according to Charts A, B, and C, corresponding R_{10} esters are likely to be produced, especially in the case of the oxa-phenylene PGF-type compounds. For some of the uses described above, it is preferred that the novel Formula XIII-to-XXVIII oxa-phenylene prostaglandin-like compounds of this invention be in free acid form, or in salt form which requires the free acid as a starting material. The PGF-esters of Formulas XVII to XX and the PGB-type compounds of Formulas XXV to XXVIII are easily hydrolyzed or saponified to the free acids by the usual known procedures, especially when R_1 (R_{10}) is alkyl of one to 4 carbons, inclusive, preferably methyl or ethyl.

On the other hand, the PGE type esters of Formulas XIII to XVI and the PGA type esters of Formulas XXI to XXIV are difficult to hydrolyze or saponify without causing unwanted structural changes in the desired acids. There are two other procedures to make the free acid forms of these Formula XIII-to-XVI and XXI-to-XXIV compounds.

One of those procedures is applicable mainly in preparing the free acids from the corresponding alkyl esters wherein the alkyl group contains one to 8 carbon atoms, inclusive. That procedure comprises subjecting the alkyl ester corresponding to Formulas XIII to XVI and XXI to XXIV to the acylase enzyme system of a microorganism species of Subphylum 2 of Phylum III, and thereafter isolating the acid. See West Germany Offenlegungsschrift No. 1,937,678; reprinted in Farmdoc Complete Specifications, Book No. 13, No. 6863 R, Week R5, March 18, 1970 and British Patent Specification No. 1,249,659.

This enzymatic hydrolysis is also applicable to the Formula XVII-to-XX PGF-type alkyl esters and the Formula XXV-to-XXVII PGB-type alkyl esters.

Another procedure for making the free acids of Formula XIII-to-XVI PGE-type compounds and Formula XXI-to-XXIV PGA-type compounds involves treatment of certain haloethyl esters of those acids with zinc metal and an alkanoic acid of 2 to 6 carbon atoms, preferably acetic acid. Those haloethyl esters are the esters wherein R_{10} is ethyl substituted in the β-position with 3 chloro, 2 or 3 bromo, or one, 2, or 3 iodo. Of those haloethyl radicals, β,β,β-trichloroethyl is preferred. Zinc dust is preferred as the physical form of the zinc. Mixing the haloethyl ester with the zinc dust at about 25°C. for several hours usually causes substantially complete replacement of the haloethyl radical of the Formula XIII-to-XVI or XXI-to-XXIV ester with hydrogen. The free acid is then isolated from the reaction mixture by procedures known to the art. This procedure is also applicable to the production of Formula XVII-to-XX PGF-type free acids or Formula XXV-to-XXVIII PGB-type free acids.

Formula-XXX cyclic ketals and Formula XXXVII olefins wherein R_{10} is haloethyl as above defined are necessary as intermediates for this route to the final PGE, PGF, PGA, and PGB type free acids. These Formula-XXX and -XXXVII haloethyl ester intermediates can be prepared by alkylation of cyclic ketal XXIX (Chart D) or olefin XXXVI (Chart E), respectively, with the appropriate Formula XLVI-to-XLIX alkylating agent wherein R_{10} is haloethyl as above defined. However, preferred routes of the Formula-XXX and -XXXVII haloethyl ester intermediates are shown in Charts F and G.

In Charts F and G, G, J, R_2, R_3, R_4, R_{11}, R_{12}, Z, and ~ are as defined above. Haloethyl represents ethyl substituted in the β-position with 3 chloro, 2 or 3 bromo,

or 1, 2, or 3 iodo, preferably —CH_2CCl_3. R_{15} represents alkyl of one to 4 carbon atoms, inclusive, preferably methyl or ethyl.

Compound LX in Chart F is within the scope of compound XXX in Chart D. Compound LXVI in Chart G is within the scope of compound XXXVII in Chart E. Ketones LX and XLVI are reduced to corresponding hydroxy compounds LXI and LXVII, respectively, with a carbonyl reducing agent, e.g., sodium borohydride, as described above in discussion of Chart A. Then, hydroxy esters LXI and LXVII are saponified by known procedures to hydroxy acids LXII and LXVIII, respectively. These two hydroxy acids are transformed to keto haloethyl esters LXV and LXXI, respectively, by oxidation of the hydroxy group to keto and esterification of the carboxyl group to —COO-haloethyl. As shown in Charts F and G, these two reactions are carried out in either order. However, it is preferred to oxidize first and then esterify.

CHART F

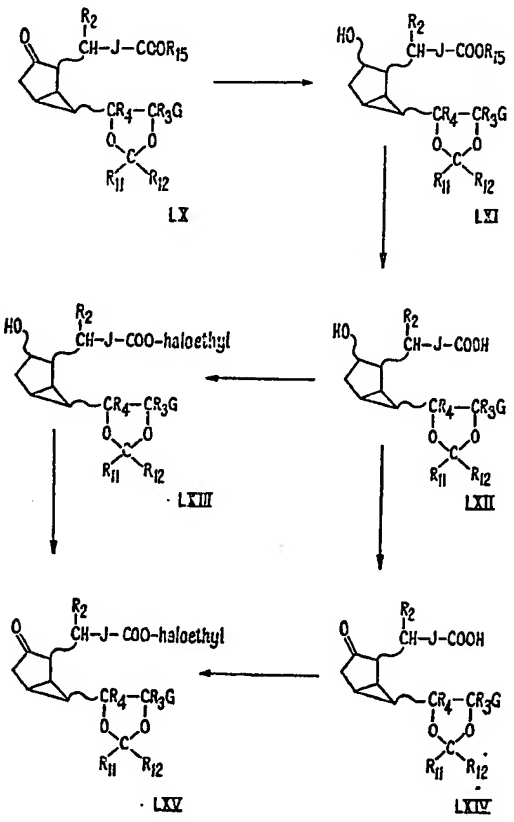
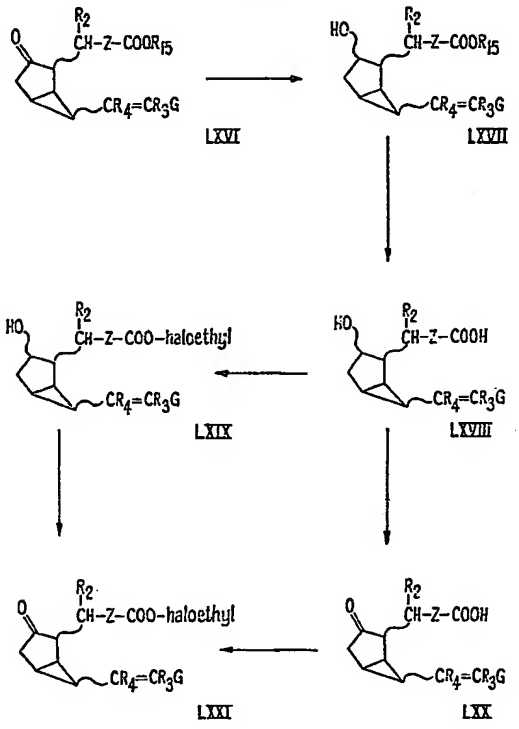


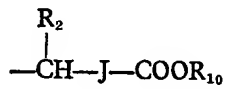
CHART G



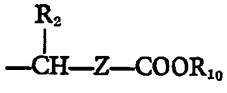
Hydroxy acids LXII and LXVIII are oxidized to keto acids LXIV and LXX, respectively, and hydroxy haloesters LXIII and LXIX are oxidized to keto haloesters LXV and LXXI, respectively, by reaction with an oxidizing agent which does not attack other parts of these molecules, especially the cyclic ketal group of compounds LXII and LXIII or the ethylenic linkage of compounds LXVIII and LXIX. An especially useful reagent for this purpose is the Jones reagent, i.e., acidic chromic acid. Acetone is a suitable diluent for this purpose, and a slight excess of oxidant and temperatures at least as low as about 0°C., preferably −10° to −20°C. should be used. The oxidation proceeds rapidly and is usually complete in 5 to 30 minutes. Excess oxidant is destroyed, for example, by addition of a lower alkanol, advantageously isopropyl alcohol, and the acid is isolated by conventional methods, for example, by extraction with a suitable solvent, e.g., diethyl ether. Other oxidizing agents can also be used. Examples are mixtures of chromium trioxide and pyridine or mixtures of dicylcohexylcarbodiimide and dimethyl sulfoxide. See, for example, J. Am. Chem. Soc. 87, 5661 (1965).

Haloethyl esters LXIII, LXV, LXIX, and LXXI are prepared by reacting acids LXII, LXIV, LXVIII, and LXX, respectively, with the appropriate haloethanol, e.g., β,β,β-trichloroethanol, in the presence of a carbodiimide, e.g., N,N′-dicyclohexylcarbodiimide, and a base, e.g., pyridine, preferably in the presence of an inert liquid diluent, e.g., dichloromethane, for several hours at about 25°C.

As described above, the alkylations of cyclic ketal XXIX to XXX (Chart D) and olefin XXXVI to XXXVII (Chart E) usually produce mixtures of alpha and beta alkylation products with respect to the



and



moieties. Also as described above, those two isomers lead to different final products, alpha leading to the PG-type series, and beta leading to the 8-iso-PG-type series. If a compound in one or the other of those two series is preferred, there are two methods for favoring production of the preferred final product.

One of those methods involves isomerization of the final product of Formulas XIII to XXVIII. Either the alpha isomer of a Formula XIII-to-XXVIII compound, ester or free acid, or the corresponding beta isomer is maintained in an inert liquid diluent in the range 0° to 80°C. and in the presence of a base characterized by its water solution having a pH below about 10 until a substantial amount of the isomer has been isomerized to the other isomer, i.e., alpha to beta or beta to alpha. Preferred bases for this purpose are the alkali metal salts of carboxylic acids, especially alkanoic acids of 2 to 4 carbon atoms, e.g., sodium acetate. Examples of useful inert liquid diluents are alkanols of one to 4 carbon atoms, e.g., ethanol. This reaction at about 25° takes one to 20 days. Apparently an equilibrium is established. The mixtures of the two isomers, alpha and beta, are separated from the reaction mixture by known procedures, and then the two isomers are separated from each other by known procedures, for example, chromatography, recrystallization, or a combination of those. The less preferred isomer is then subjected to the same isomerization to produce more of the preferred isomer. In this manner by repeated isomerizations and separations, substantially all of the less preferred isomer of the Formula XIII-to-XXVIII compound is transformed to more preferred isomer.

The second method for favoring production of a preferred Formula XIII-to-XXVIII isomer involves any one of the keto intermediates of Formulas XXX, XXXI, XXXVII, or XXXVIII (Charts D and E). Either the alpha form or the beta form of one of those intermediates is transformed to a mixture of both isomers by maintaining one or the other isomer, alpha or beta, in an inert liquid diluent in the presence of a base and in range 0° to 100°C. until a substantial amount of the starting isomer has been isomerized to the other isomer. Preferred bases for this isomerization are alkali metal amides, alkali metal alkoxides, alkali metal hydrides, and triarylmethyl alkali metals. Especially preferred are alkali metal tert-alkoxides of 4 to 8 carbon atoms, e.g., potassium tert-butoxide. This reaction at about 25°C. proceeds rapidly (one minute to several hours). Apparently an equilibrium mixture of both isomers is formed, starting with either isomer. The isomer mixtures in the equilibrium mixture thus obtained are isolated by known procedures, and then the two isomers are separated from each other by known procedures, for example, chromatography. The less preferred isomer is then subjected to the same isomerization to produce more of the preferred isomer. In this manner, by repeated isomerizations and separations, substantially all of the less preferred isomer of any of these intermediates is transformed to the more preferred isomer. Cyclic ketalketone intermediates of Formula XXX are preferred over the other intermediates for this isomerization procedure.

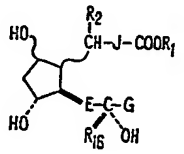
The novel oxa-phenylene PGE, PGF, PGA, and PGB type compounds of Formula XIII to XXVIII wherein R_3 is alkyl of one to 4 carbon atoms, inclusive, preferably methyl or ethyl, are preferred over the corresponding oxa-phenylene PGE, PGF, PGA, and PGB type compounds in which R_3 is hydrogen for the above-described pharmacological purposes.

The 15-alkyl prostaglandin analogs are surprisingly and unexpectedly more useful than the corresponding 15-hydrogen compounds for the reason that they are substantially more specific with regard to potency in causing prostaglandin-like biological responses, and have substantially longer duration of biological activity. For that reason, fewer and smaller doses of these 15-alkyl prostaglandin analogs are needed to attain the desired pharmacological results.

Although the above-mentioned 15-alkyl compounds are produced by the methods outlined above in Charts A—E, the preferred methods are set forth in Chart H and I as follows.

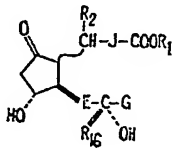
In Chart H is shown the transformation of 15-alkyl PGF-type acids and alkyl esters to the corresponding PGE-type acids and alkyl esters by oxidation. For this purpose, an oxidizing agent is used which selectively oxidizes secondary hydroxy groups to carbonyl groups in the presence of carbon-carbon double and triple bonds. Formula LXXII in Chart H includes optically active compounds as shown and racemic com-

CHART H



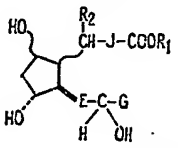
LXXIII

(Oxidation)



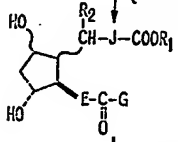
LXXIII

CHART I



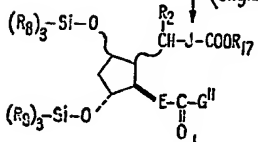
LXXIV

(oxidation)



LXXV

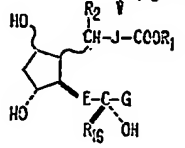
(silylation)



LXXVI

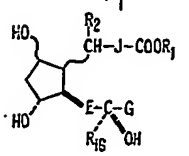
$R_{16}MgHal$

(hydrolysis)



LXXVII

+



LXXVII

pounds thereof, and also the 15-epimers of both of those, i.e., wherein the configuration at C-15 is β rather than α as shown. Also in Chart H, E, G, J, R_1, and R_2 are as defined above, and R_{16} is alkyl of one to 4 carbon atoms.

For the transformations of Chart H, the β-hydroxy isomers of reactant LXXII are preferred starting materials when the carboxyl side chain is alpha, although the corresponding α-hydroxy isomers are also useful for this purpose.

Oxidation reagents useful for the transformation set forth in Chart H are known to the art. An especially useful reagent for this purpose is the Jones reagent, i.e., acidified chromic acid. See J. Chem. Soc. 39 (1946). A slight excess beyond the amount necessary to oxidize one of the secondary hydroxy groups of the Formula-LXXII reactant is used. Acetone is a suitable diluent for this purpose. Reaction temperatures at least as low as about 0°C. should be used. Preferred reaction temperatures are in the range −10° to −50°C. The oxidation proceeds rapidly and is usually complete in 5 to 20 minutes. The excess oxidant is destroyed, for example by addition of a lower alkanol, advantageously, isopropyl alcohol, and the Formula-LXXIII PGE-type product is isolated by conventional methods.

Examples of other oxidation reagents useful for the Chart H transformations are silver carbonate on Celite—Registered Trade Mark—(Chem. Commun. 1102 (1969)), mixtures of chromium trioxide and pyridine (Tetrahedron Letters 3363 (1968), J. Am. Chem. Soc. 75, 422 (1953), and Tetrahedron, 18, 1351 (1962)), mixtures of sulfur trioxide in pyridine and dimethyl sulfoxide (J. Am. Chem. Soc. 89, 5505 (1967)), and mixtures of dicyclohexylcarbodiimide and dimethyl sulfoxide (J. Am. Chem. Soc. 87, 5661 (1965)).

The novel 15-alkyl oxa-phenylene PGF_α- and PGF_β-type acids and esters of Formulas XVII to XX wherein R_3 is one to 4 carbon atoms, inclusive, are preferably prepared from the corresponding 15-hydrogen compounds by the sequence of transformations shown in Chart I, wherein Formulas LXXIV to LXXVIII, inclusive, include optically active and racemic compounds thereof and also the 15-epimers of both of these. Also in Chart I, R_{16} is alkyl of one to 4 carbon atoms, inclusive, and E, G, Hal, J, R_1, R_2, and ~ are as heretofore defined; G'' in Formula LXXVI is the same as G except that T is replaced by T'', wherein T'' is the same as T above except that, in R_9, $-Si(R_8)_3$ replaces hydrogen. Also in Chart I, R_8 is alkyl of one to 4 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, or phenyl substituted with one or 2 fluoro, chloro, or alkyl of one to 4 carbon atoms, inclusive, and R_{17} is R_1 as defined above or silyl of the formula—Si—$(R_8)_3$ wherein R_8 is as defined above. The various R_8's of a $-Si(R_8)_3$ moiety are alike or different. For example, a $-Si(R_8)_3$ can be trimethylsilyl, dimethylphenylsilyl, or methylphenylbenzylsilyl. Examples of alkyl of one to 4 carbon atoms, inclusive, are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl. Examples of aralkyl of 7 to 12 carbon atoms, inclusive, are benzyl, phenethyl, α-phenylethyl, 3-phenylpropyl, α-naphthylmethyl, and 2-(β-naphthyl)ethyl. Examples of phenyl substituted with one or 2 fluoro, chloro, or alkyl of one to 4 carbon atoms, inclusive, are *p*-chlorophenyl, *m*-fluorophenyl, o-tolyl, 2,4-dichlorophenyl, *p*-tert-butylphenyl, and 4-chloro-2-methyl-phenyl.

In Chart I, the final PGF_α and PGF_β-type products are those encompassed by Formulas LXXVII and LXXVIII, respectively.

The initial optically active or racemic reactants of Formula LXXIV in Chart I i.e., the oxa-phenylene PGF_1-, PGF_2-, 5,6-dehydro-PGF_2-, and dihydro-PGF_1-type compounds in their α and β forms, and their esters, are prepared by methods described herein. Thus, racemic oxa-phenylene dihydro-$PGF_{1\alpha}$- and -$PGF_{1\beta}$-type compounds, and their esters are prepared by catalytic hydrogenation of the corresponding racemic oxa-phenylene $PGF_{1\alpha}$ or $PGF_{2\alpha}$, and $PGF_{1\beta}$ or $PGF_{2\beta}$ type compounds, respectively, e.g. in the presence of 5% palladium-on-charcoal catalyst in ethyl acetate solution at 25°C. and one atmosphere pressure of hydrogen.

The heretofore-described acids and esters of Formula LXXIV are transformed to the corresponding intermediate 15-dehydro acids and esters of Formula LXXV, by oxidation with reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, activated manganese dioxide, or nickel peroxide (see Fieser et al., "Reagents for Organic Syntheses," John Wiley & Sons, Inc., New York, N.Y. pp. 215, 637, and 731). Alternatively, and especially for the Formula-LXXIV reactants wherein E is $-CH_2CH_2$ and J is L as defined above, these oxidations are carried out by oxygenation in the presence of the 15-hydroxyprostaglandin dehydrogenase of swine lung (see Arkiv för Kemi 25, 293 (1966)). These reagents are used according to procedures known in the art. See, for example, J. Biol. Chem. 239, 4097 (1964).

Referring again to Chart I, the intermediate compounds of Formula LXXV are transformed to silyl derivatives of Formula LXXVI by procedures known in the art.

See, for example, Pierce, "Silylation of Organic Compounds," Pierce Chemical Co., Rockford, III. (1968). Both hydroxy groups of the Formula-LXXV reactants are thereby transformed to —O—$Si(R_8)_3$ radicals wherein R_8 is as defined above, and sufficient of the silylating agent is used for that purpose according to known procedures. When R_1 in the Formula-LXXV intermediate is hydrogen, the —COOH radical thereby defined is simultaneously transformed to —COO—$Si(R_8)_3$, additional silylating agent being used for this purpose. This latter transformation is aided by excess silylating agent and prolonged treatment. Likewise, when R_9 in T of the Formula-LXXV intermediate is hydrogen, the phenolic hydroxyl thereby defined is simultaneously transformed to —O—$Si(R_8)_3$ in the silylation step. G'' in Formula LXXVI, therefore is the same as G except that T is replaced by T'', wherein T'' is the same as T above except that, in R_9, —$Si(R_8)_3$ replaces hydrogen. When R_1 in Formula LXXV is alkyl, then R_{17} in Formula LXXVI will also be alkyl. The necessary silylating agents for these transformations are known in the art or are prepared by methods known in the art. See, for example, Post, "Silicones and Other Organic Silicon Compounds," Reinhold Publishing Corp., New York, N.Y. (1949).

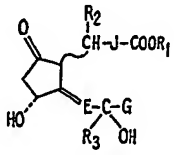
Referring again to Chart I the intermediate silyl compounds of Formula LXXVI are transformed to the final compounds of Formulas LXXVII and LXXVIII by first reacting the silyl compound with a Grignard reagent of the formula $R_{16}MgHal$ wherein R_{16} is as defined above, and Hal is chloro, bromo, or iodo. For this purpose, it is preferred that Hal be bromo. This reaction is carried out by the usual procedure for Grignard reactions, using diethyl ether as a reaction solvent and saturated aqueous ammonium chloride solution to hydrolyze the Grignard complex. The resulting disilyl, trisilyl, or tetrasilyl tertiary alcohol is then hydrolyzed with water to remove the silyl groups. For this purpose, it is advantageous to use a mixture of water and sufficient of a water-miscible solvent, e.g., ethanol to give a homogenous reaction mixture. The hydrolysis is usually complete in 2 to 6 hours at 25°C., and is preferably carried out in an atmosphere of an inert gas, e.g., nitrogen or argon.

The mixture of 15-α and 15-β isomers obtained by this Grignard reaction and hydrolysis is separated by procedures known in the art for separating mixtures of prostanoic acid derivatives, for example, by chromatography on neutral silica gel. In some instances, the lower alkyl esters, especially the methyl esters of a pair of 15-α and 15-β isomers are more readily separated by silica gel chromatography than are the corresponding acids. In those cases, it is advantageous to esterify the mixture of acids as described below, separate the two esters, and then, if desired, saponify the esters by procedures known in the art for saponification of prostaglandins F.

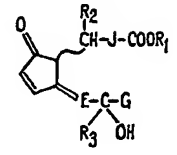
Although Formula-LXXVII and -LXXVIII compounds wherein E is —CH_2CHR_4— and J is L as defined above may be produced according to the processes of Chart I, it is preferred to produce those novel dihydro-PGF_1 analogs by hydrogenation of one of the corresponding unsaturated compounds, i.e., a compound of Formula LXXVII or LXXVIII wherein E is *trans* —CH=CR_4— and J is either L, —CH=CH—M—, —C≡C—M—, M being defined above. This hydrogenation is advantageously carried out catalytically, for example, in the presence of a 5% palladium-on-charcoal catalyst in ethyl acetate solution at 25°C. and one atmosphere pressure of hydrogen.

The novel 15-alkyl oxa-phenylene PGA-type and PGB-type acids and esters of Formulas XXI to XXVIII are prepared from the 15-alkyl oxa-phenylene PGE compounds, heretofore described, by dehydrations and double bond migrations previously described, as shown in Chart A. Likewise the 15-alkyl PGB-type compounds are prepared by contacting the 15-alkyl PGA-type compounds with base. For the transformation of the 15-alkyl PGE-type compounds to the 15-alkyl PGA-type compounds of this invention (Chart J), it is preferred that a dehydrating agent be used which removes the hydroxy group from the alicyclic ring in the presence of a hydroxy group on a tertiary carbon atom. Formula LXXIX as shown includes optically active compounds and racemic compounds thereof, and also the 15-epimers of both of those. Any of the known substantially neutral dehydrating agents is used for these reactions. See Fieser et al., cited above. Preferred dehydrating agents are mixtures of at least an equivalent amount of a carbodiimide and a catalytic amount of a copper (II) salt. Especially preferred are mixtures of at least an equivalent amount of N,N'-dicyclohexylcarbodiimide and a catalytic amount of copper (II) chloride. An equivalent amount of a carbodiimide means one mole of the carbodiimide for each mole of the Formula-LXXIX reactant. To ensure completeness of the reaction, it is advantageous to use an excess of the carbodiimide, i.e., 1.5 to 5 or even more equivalents of the carbodiimide.

CHART J



LXXIX



LXXX

The dehydration is advantageously carried out in the presence of an inert organic diluent which gives a homogeneous reaction mixture with respect to the Formula-LXXIX reactant and the carbodiimide. Diethyl ether is a suitable diluent. It is advantageous to carry out the dehydration in an atmosphere of an inert gas, e.g., nitrogen, helium, or argon. The time required for the dehydration will depend in part on the reaction temperature. With the reaction temperature in the range 20° to 30° C., the dehydration usually takes place in 40 to 60 hours.

The Formula-LXXX product is isolated by methods known in the art, e.g., filtration of the reaction mixture and evaporation of the filtrate. The product is then purified by methods known in the art, advantageously by chromatography on silica gel.

The final Formula XIII-to-XXVIII compounds prepared by the processes of this invention, in free acid form, are transformed to pharmacologically acceptable salts by neutralization with appropriate amounts of the corresponding inorganic or organic base, examples of which correspond to the cations and amines listed above. These transformations are carried out by a variety of procedures known in the art to be generally useful for the preparation of inorganic, i.e., metal or ammonium, salts, amine acid addition salts, and quaternary ammonium salts. The choice of procedure depends in part upon the solubility characteristics of the particular salt to be prepared. In the case of the inorganic salts, it is usually suitable to dissolve the Formula XIII-to-XXVIII acid in water containing the stoichiometric amount of a hydroxide, carbonate, or bicarbonate corresponding to the inorganic salt desired. For example, such use of sodium hydroxide, sodium carbonate, or sodium bicarbonate gives a solution of the sodium salt. Evaporation of the water or addition of a water-miscible solvent of moderate polarity, for example, a lower alkanol or a lower alkanone, gives the solid inorganic salt if that form is desired.

To produce an amine salt, the Formula XIII-to-XXVIII acid is dissolved in a suitable solvent of either moderate or low polarity. Examples of the former are ethanol, acetone, and ethyl acetate. Examples of the latter are diethyl ether and benzene. At least a stoichiometric amount of the amine corresponding to the desired cation is then added to that solution. If the resulting salt does not precipitate, it is usually obtained in solid form by addition of a miscible diluent of low polarity or by evaporation. If the amine is relatively volatile, an excess can easily be removed by evaporation. It is preferred to use stoichiometric amounts of the less volatile amines.

Salts wherein the cation is quaternary ammonium are produced by mixing the formula XIII-to-XXVIII acid with the stoichiometric amount of the corresponding quaternary ammonium hydroxide in water solution, followed by evaporation of the water.

The final Formula XIII-to-XXVIII acids or esters prepared by the processes of this invention are transformed to lower alkanoates by interaction of the Formula XIII-to-XXVIII hydroxy compound with a carboxyacylating agent, preferably the anhydride of a lower alkanoic acid, i.e., an alkanoic acid of one to 8 carbon atoms, inclusive. For example, use of acetic anhydride gives the corresponding diacetate. Similar use of propionic anhydride, isobutyric anhydride, and hexanoic acid anhydride gives the corresponding carboxacylates.

The carboxyacylation is advantageously carried out by mixing the hydroxy compound and the acid anhydride, preferably in the presence of a tertiary amine such as pyridine or triethylamine. A substantialy excess of the anhydride is used, preferably 10 to 10,000 moles of anhydride per mole of the hydroxy compound reactant. The excess anhydride serves as a reaction diluent and solvent. An inert organic diluent, for example, dioxane, can also be added. It is preferred to use enough of the tertiary amine to neutralize the carboxylic acid produced by the reaction, as well as any free carboxyl groups present in the hydroxy compound reactant.

The carboxyacylation reaction is preferably carried out in the range 0° to 100° C. The necessary reaction time will depend on such factors as the reaction temperature, and the nature of the anhydride and tertiary amine reactants. With acetic anhydride, pyridine, and a 25° C. reaction temperature, a 12 to 24-hours reaction time is used.

The carboxyacylated product is isolated from the reaction mixture by convention methods. For example, the excess anhydride is decomposed with water, and the resulting mixture acidified and then extracted with a solvent such as diethyl ether. The desired carboxyacylate is recovered from the diethyl ether extract by evaporation. The carboxyacylate is then purified by conventional methods, advantageously by chromatography.

By this procedure, the Formula XIII-to-XVI PGE-type compounds are transformed to dialkanoates, the Formula XVII-to-XX PGF-type compounds are transformed to trialkanoates, and the Formula XXI-to-XXVIII PGA-type and PGB-type compounds are transformed to monoalkanoates.

When a PGE-type dialkanoate is transformed to a PGF-type compound by carbonyl reduction as shown in Chart A, a PGF-type dialkanoate is formed and is used for the above-described purposes as such or is transformed to a trialkanoate by the above-described procedure. In the latter case, the third alkanoyloxy group can be the same as or different from the two alkanoyloxy group present before the carbonyl reduction.

Molecules of each of the compounds encompassed by Formulas XIII to XXVIII and, except for XXXVI and XLIII, of each intermediate formula each have at least one center of asymmetry, and each can exist in racemic form and in either enantiomeric form, i.e., d and l. A formula accurately defining the d form would be the mirror image of the formula which defined the l form. Both formulas are necessary to define accurately the corresponding racemic form. For convenience, the various formulas are to be construed as including racemic, d, and l compounds.

When an optically active (d or l) final compound is desired, that is made by resolution of the racemic compound or by resolution of one of the asymmetric racemic intermediates. These resolutions are carried out by procedures known in the art. For example, when final compound XIII to XXVIII is a free acid, the dl form thereof is resolved into the d and l forms by reacting said free acid by known general procedures with an optically active base, e.g., brucine or strychnine, to give a mixture of two diastereoisomers which are separated by known general procedures, e.g., fractional crystallization, to give the separate diastereoisomeric salts. The optically active acid of Formula XIII to XXVIII is then obtained by treatment of the salt with an acid by known general procedures. Alternatively, the free acid form of cyclic ketal XXX, olefin XXXVII or glycols XXI or XXXVIII is resolved into separate d and l forms and then esterified and transformed further to the corresponding optically active form of the final product XIII to XXVIII as described above.

Alternatively, bicyclo ketone reactants XXXI or XXXVIII, in *exo* or *endo* form, are transformed to ketals with an optically active 1,2-glycol, e.g., D-(—)-2,3-butanediol, by reaction of said 1,2-glycol with the Formula-XXXI or -XXXVIII compound in the presence of a strong acid, e.g., *p*-toluenesulfonic acid. The resulting ketal is a mixture of diastereoisomers which is separated into the d and l diastereoisomers, each of which is then hydrolyzed with an acid, e.g., oxalic acid, to the original

keto compound, now in optically active form. These reactions involving optically active glycols and ketals for resolution purposes are generally known in the art. See, for example, Chem. Ind. 1664 (1961) and J. Am. Chem. Soc. 84,2938 (1962). Dithiols may be used instead of glycols.

The invention can be more fully understood by the following Examples 3, 4, 5, 8, 16 to 25 and 27 to 33. The preparations and Examples 1, 2, 6, 7, 9 to 15 and 26 are directed to the preportion of intermediates.

All temperatures are in degrees centigrade.

Infrared absorption spectra are recorded on a Perkin-Elmer Model 421 infrared spectrophotometer. Except when specified otherwise, undiluted (neat) samples are used.

Ultraviolet spectra are recorded on a Cory Model 15 spectrophotometer.

NMR spectra are recorded on a Varian A-60 spectrophotometer on deuterochloroform solutions with tetramethylsilane as an internal standard (downfield).

Mass spectra are recorded on an Atlas (Registered Trade Mark) CH-4 mass spectrometer with a TO-4 source (ionization voltage 70 ev).

The collection of chromatographic eluate fractions starts when the eluant front reaches the bottom of the column.

"Brine", herein, refers to an aqueous saturated sodium chloride solution.

Preparation 1

dl-*Endo*-6-(1-heptenyl)-3-(1-pyrrolidinyl)-bicyclo[3.1.0]hex-2-ene.

A solution of Formula-XXXVI endo-6-(*cis*- and *trans*-1-heptenyl)bicyclo[3.1.0] hexan-3-one (see Example 29 of West Germany Offenlagungsschrift No. 1,937,912, cited above) (15 g.), 25 ml. of pyrrolidine, and 200 ml. of benzene is heated under reflux while removing the water formed by distillation. After 2 hrs. the benzene is replaced by 50 ml. of toluene which is then removed *in vacuo* to give the *endo*-6-(1-heptenyl) - 3 - (1 - pyrrolidinyl) - bicyclo[3.1.0]hex - 2 - ene. This material gives an infrared spectrum having absorption attributable to the enamine double bond at 1610 cm^{-1} and free of carbonyl absorption.

Preparation 2

Methyl[*m* - (Chloromethyl)phenoxy]acetate (Formula XLVI: C_gH_{2g} and C_pH_{2p} are valence bonds in meta relationship, C_qH_{2q} is methylene, Hal is chloro, R_2 is hydrogen, and R_{10} is methyl).

a. (*m*-Formylphenoxy)acetic Acid. To a solution of *m*-hydroxybenzaldehyde (48.8 g.) and sodium hydroxide (16.16 g.) in 500 ml. of water is added a solution prepared from chloroacetic acid (75 g.) and sodium hydroxide (32 g.) in 100 ml. of water. The mixture is heated under reflux for 2 hrs., cooled, and the pH is adjusted to pH 1 or 2. The mixture is extracted with dichloromethane-ether and the extract is dried and concentrated. The solid is taken up in saturated aqueous sodium bicarbonate, extracted with ether and the aqueous phase is made acidic. The aqueous phase is extracted with dichloromethane. The organic layer is concentrated and the residue is recrystallized from water to give (*m*-formylphenoxy)acetic acid (34.0 g.) m.p. 114—117°.

b. Methyl(*m*-Formylphenoxy)acetate. A solution of (*m*-formylphenoxy)acetic acid (30.0 g.) in 400 ml. of diethyl ether-tetrahydrofuran is treated with an excess of ethereal diazomethane generated from N - methyl - N' - nitro - N - nitro - soguanidine (32.5 g.) and 200 ml. of 30% potassium hydroxide. The organic extract is washed with 5% sodium hydroxide, dried and concentrated to give methyl(*m*-formylphenoxy)acetate (17 g.), as a light yellow oil.

c. Methyl[*m*-(Hydroxymethyl)phenoxy]acetate. A solution of methyl *m*-(formylphenoxy)acetate (30.0 g.) in 200 ml. of methanol, cooled in an ice bath to 0°, is treated with sodium borohydride (1.55 g.) in 30 ml. of cold water. After the addition, stirring is continued for 20 min., the methanol is removed, and 60 ml. of brine is added. The aqueous phase is extracted with ether and the ether solution is washed, first with 5% aqueous hydrochloric acid, then brine, and dried. Removal of the solvent yields methyl[*m*-(hydroxymethyl)phenoxy]acetate (27.0 g.).

d. Methyl[*m*-(Chloromethyl)phenoxy]acetate. To methyl [*m*-(hydroxymethyl) phenoxy]acetate (27.0 g.) is added 20 ml. of thionyl chloride with stirring. Following the addition, the reaction mixture is stirred at 25° for 30 min. and at reflux for 30 min. After cooling the reaction mixture, it is dissolved in ether and washed carefully with water, saturated aqueous sodium bicarbonate and brine. The organic layer is dried, concentrated and distilled to give the desired Formula-XLVI title compound, methyl[*m*-(chloromethyl)phenoxy]acetate (11.0 g.) b.p. 98—110°/0.03 mm.

Following the procedures of Preparation 2, but replacing chloroacetic acid with 3-chloropropionic acid, there is obtained, successively, 3 - [(*m* - formyl)phenoxy] propionic acid and its methyl ester, methyl 3-[*m*-(hydroxymethyl)phenoxy]propionate, and the Formula-XLVI compound, methyl 3-[*m*-(chloromethyl)phenoxy]propionate.

Alternatively, Michael addition of *m*-hydroxybenzaldehyde to methyl acrylate, with base catalysis, and reduction of the product with sodium borohydride gives methyl 3-[*m*-(hydroxymethyl)phenoxy]propionate.

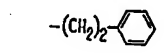
Preparation 3

Ethyl[*o* - (Bromomethyl)benzyloxy]acetate (Formula XLVI: C_eH_{2e} is a valence bond, C_pH_{2p} and C_qH_{2q} are methylene, C_gH_{2g} and C_pH_{2p} are in ortho relationship, Hal is bromo, R_2 is hydrogen, and R_{10} is ethyl).

To a mixture of α,α'-dibromo-*o*-xylene (100 g.), ethyl glycolate (47 g.), and dimethylformamide (500 ml.) is added with stirring over a 1-hour period at 0—5° C., 18 g. of 57% sodium hydride. The mixture is stirred for 16 hrs. at about 25° C. and is then concentrated on a rotating evaporation at 40—50° C. under vacuum. The residue is diluted with one liter of a mixture of isomeric hexanes (Skellysolve B) and diethyl ether (1:2 by volume) and the organic solution is washed successively with dilute hydrochloric acid, dilute potassium hydroxide solution, water, and brine, and is finally dried and concentrated. The residue is chromatographed on a column prepared by wet-packing 3 kg. of silica gel (Brinkman) with 6 l. of 15% ethyl acetate in Skellysolve B and 30 ml. of absolute ethanol. Gradient elution of the column with 16 l. of 15—35% ethyl acetate in Skellysolve B gives fractions of 400 ml. each of which are combined on the basis of thin layer chromatography (TLC). From fractions 18—27 there is obtained 35 g. of the desired Formula-XLVI title compound, ethyl [*o*-(bromomethyl)benzyloxy]acetate. This material has $\lambda_{max.}$ in ethanol at 231 mμ (ε 7550) with shoulders at 272 (ε 700) and 278 mμ (ε 462). It has key absorptions in its NMR spectrum at about 7.3 (apparent single), 4.7 (singlet), 4.64 (singlet), 4.06 (singlet), 4.0—4.35 (quartet), and 1.1—1.34 (triplet) δ. It has mass spectral peaks at 206, 199, 201, 185, and 183.

Preparation 4

Endo - 6 - (4 - phenyl - *cis* - 1 - butenyl) - bicyclo[3.1.0]hexan - 3 - one (Formula XXXVI: [G is



R_2 and R_4 are hydrogen; and ~ is *endo*).

a. There is first prepared (3-phenylpropyl)triphenylphosphonium bromide. A solution of 597.3 g. of 1 - bromo - 3 - phenylpropane and 786 g. of triphenylphosphine in 1500 ml. of toluene is heated at reflux under nitrogen for 16 hrs., then the mixture is cooled and the solid product is separated by filtration. The solid is then slurried with toluene in a Waring blender, separated by filtration, and dried for 18 hrs. at 70° C. under reduced pressure to give 1068 g. of (3-phenylpropyl)triphenylphosphonium bromide; m.p. 210.5—211.5° C.

b. A suspension of 314 g. of (3-phenylpropyl)triphenylphosphonium bromide in 3 l. of benzene is stirred at room temperature (25° C.) under nitrogen, and 400 ml. of 1.6 M butyllithium in hexane is added over a 20 min. period. The mixture is heated at 35° C. for 30 minutes, then is cooled to —15° C. and a solution of 100 g. of *endo* - bicyclo[3.1.0]hexan - 3 - ol - 6 - carboxaldehyde 3 - tetrahydropyran - 2′-yl ether in 200 ml. of benzene is added over a 30-min. period. This mixture is heated at 70° C. for 2.5 hrs., cooled, and filtered. The filtrate is washed three times with water, dried over sodium sulfate, and evaporated to give 170 g. of crude *endo*-6 - (4 - phenyl - *cis* - 1 - butenyl) - bicyclo[3.1.0]hexan - 3 - ol 3 - tetrahydropyran-2′-yl ether.

A solution of 340 g. (two runs) of this crude *endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - bicyclo - [3.1.0]hexan - 3 - ol 3 - tetrahydropyran - 2′ - yl ether and 20 g. of oxalic acid in 3600 ml. of methanol is heated at reflux for 3.5 hrs. The mixture is cooled and the methanol is evaporated under reduced pressure. The residue is mixed with methylene chloride, and the methylene chloride solution is washed with aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to give 272 g. of the *endo*-6-(4-phenyl-*cis*-1-butenyl)-bicyclo[3.1.0]hexan-3-ol.

A solution of 93 g. of the above *endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) bicyclo[3.1.0]hexan-3-ol in 2570 ml. of acetone is cooled to −5° C. and 160 ml. of Jones reagent (in the proportions 42 g.) of chromic anhydride, 120 ml. of water, and 34 ml. of concentrated sulfuric acid) is added over a period of 30 min. while cooling to maintain a temperature of −5°C. The mixture is allowed to stand for 10 min. longer; then 100 ml. of isopropyl alcohol is added and the mixture is swirled for 5 min. The mixture is then diluted with 6 l. of water and extracted several times with methylene chloride. The organic layers are separated, washed with dilute hydrochloric acid, water, dilute aqueous sodium bicarbonate, and brine, then are dried over sodium sulfate, combined and evaporated to give 83 g. of crude *endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - bicyclo[3.1.0]hexa - 3 - one.

Crude *endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - bicyclo[3.1.0] - hexan - 3 - one (162 g., two runs) is dissolved in isomeric hexanes (Skellysolve B) and chromatographed over 5 kg. of silica gel wet-packed with Skellysolve B, eluting successsively with 11 l. of Skellysolve B, 62 l. of 2.5% ethyl acetate in Skellysolve B, and 32 l. of 5% ethyl acetate in Skellysolve B. The last 8 l. of the 2.5% ethyl acetate in Skellysolve B eluates and the 32 l. of 5% ethyl acetate in Skellysolve B eluates are combined and evaporated to give 75.8 g. of the desired Formula-XXXVI title compound, *endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - bicyclo[3.1.0]hexan - 3 - one; infrared absorption at 3000, 1750, 1610, 1500, 1455, 1405, 1265, 1150, 778, 750 and 702 cm^{-1}., N.M.R. peaks at 7.18 (singlet) and 4.75—6.0 (broad multiplet) δ.

Preparation 5

Endo - 6 - (5 - phenyl - *cis* - 1 - pentenyl) - bicyclo[3.1.0]hexan - 3 - one. (Formula XXXVI: G is

R_3 and R_4 are hydrogen; and ∼ is *endo*).

a. There is first prepared (4-phenylbutyl)triphenylphosphonium bromide. A solution of 145 g. of 4-phenyl-1-bromobutane and 179 g. of triphenylphosphine in 350 ml. of toluene is heated at reflux under nitrogen for 16 hrs. The mixture is then cooled slowly and ether is added giving a precipitate of (4-phenylbutyl)triphenylphosphonium bromide which is washed thoroughly with benzene/ether and dried 18 hrs. at 50°C. under reduced pressure, 268 g., m.p. 139—140°C.

b. A suspension of 242 g. of (4-phenylbutyl)-triphenylphosphonium bromide in 2.3 l. of dry benzene at 25°C. is stirred and 300 ml. of 1.6 M butyllithium in hexane is added over a 15-min. period. The mixture is stirred at 30°C. for one hour, then is cooled to 10°C. and a solution of 75 g. of *endo* - bicyclo[3.1.0]hexan - 3 - ol - 6 - carboxaldehyde 3 - tetrahydropyran - 2′ - yl ether in 200 ml. of benzene is added over a 15-min. period. The mixture is heated at 65—70°C. for 3 hours, cooled and filtered. The filtrate is washed with water and brine, dried over sodium sulfate, and evaporated under reduced pressure to give 117 g. of crude *endo* - 6 - (5 - phenyl - *cis* - 1 - pentenyl) - bicyclo[3.1.0]hexan - 3 - ol tetrahydropyran - 2′ - yl ether showing a single spot, R_f 0.75, on thin layer chromatography with silica gel plates developed with 20% ethyl acetate in cyclohexane.

A solution of 117 g. of the above crude *endo* - 6 - (5 - phenyl - *cis* - 1 - pentenyl) - bicyclo[3.1.0]hexan - 3 - ol tetrahydropyran - 2′ - yl ether and 6 g. of oxalic acid in 2500 ml. of methanol is heated under reflux for 2.5 hrs. The methanol is then removed by distillation under reduced pressure and the residue is diluted with water and extracted with methylene chloride. The methylene chloride extracts are combined, washed with aqueous sodium bicarbonate and brine, dried over sodium sulfate and evaporated under reduced pressure to give 95.7 g. of crude *endo* - 6 - 5 - phenyl - cis - 1 - pentenyl)bicyclo - [3.1.0]hexan - 3 - ol. The entire crude product is chromatographed over 1.5 g. of silica gel wet-packed with Skellysolve B, eluting successively with 5 l. of Skellysolve B, 4 l. of 2.5%, 6 l. of 5%, 9 l. of 7.5%, 12 l. of 10%, 8 l. of 15%, 10 l. of 20% and 10 l. of 30% ethyl acetate in Skellysolve B, taking 600 ml. fractions. The last fraction of 10% ethyl acetate in Skellysolve B, all the 15% and 20% ethyl acetate in Skellysolve B eluates, and the first 3 fractions of 30% ethyl acetate in Skellysolve B are evaporated to give 60.5 g. of purified endo - 6 - (5 - phenyl - *cis* - 1 - pentenyl)bicyclo[3.1.0]hexan - 3 - ol.

A solution of 60.5 g. of the above purified alcohol in 1600 ml. of acetone is cooled to −10°C. and 103 ml. of Jones reagent is added dropwise. After addition is complete the mixture is stirred for 10 min. at 0°C. and 65 ml. of isopropyl alcohol is added. The mixture is poured into 8 l. of water and extracted several times with methylene chloride. The methylene chloride extracts are combined, washed with dilute hydrochloric acid, aqueous sodium bicarbonate and brine, dried over sodium sulfate and evaporated under reduced pressure to give 56 g. of crude *endo* - 6 - (cis - 5 - phenyl - 1 - pentenyl)bicyclo[3.1.0]hexan - 3 - one. The crude ketone is slurried in Skellysolve B and chromatographed over 2300 g. of silica gel wet packed in Skellysolve B, eluting successively with 6 l. of Skellysolve B, 16 l. of 2.5% ethyl acetate in Skellysolve B, then gradient elution with 5 l. of 2.5% and 5 l. of 5% ethyl acetate in Skellysolve B and finally 16 l. of 5% ethyl acetate in Skellysolve B, taking 625 ml. fractions. The last fraction of the gradient eluates and the first 19 fractions of 5% ethyl acetate in Skellysolve B are concentrated to give 23.6 of the Formula-XXXVI compound, *endo* - 6 - (5 - phenyl - *cis* - 1 - pentenyl)bicyclo[3.1.0]hexan - 3 - one; infrared absorption at 2980, 1745, 1600, 1490, 1450, 1260, 1145, 770, 750 and 702 cm^{-1}., N.M.R. peaks at 7.17 (singlet), 6.0—5.4 (multiplet), and 5.2—4.7 (broad multiplet) δ.

Preparation 6

Endo - 6 - (1,2 - dihydroxy - 4 - phenylbutyl) - bicyclo[3.1.0]hexan - 3 - one Acetonide (Formula XXIX wherein G is

R_3 and R_4 are hydrogen, R_{11} and R_{12} are methyl, and ∼ is *endo*).

a. There is first prepared the Formula-XLIV dihydroxy compound. To a solution of *endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - bicyclo[3.1.0]hexan - 3 - one (10.0 g., Preparation 4) in about 100 ml. tetrahydrofuran is added, with stirring, a solution of potassium chlorate (10.0 g.) and osmium tetroxide (0.65 g.) in 250 ml. of water. The mixture is stirred vigorously for 5 hrs. at 50°C. Then, the cooled mixture is concentrated under reduced pressure. The residue is extracted repeatedly with dichloromethane, and the combined extracts are dried and evaporated to give an oil. This oil is chromatographed on about 1000 g. of silica gel, and eluted successively with 3 l. of 10% ethyl acetate in a mixture of isomeric hexanes (Skellysolve B), with 5 l. of 25% ethyl acetate in Skellysolve B, and then with 50% ethyl acetate in Skellysolve B, collecting 500 ml. eluate fractions. Fractions 13—19 (50% ethyl acetate) are combined and evaporated to dryness to give *endo* - 6(1,2 - dihydroxy - 4 - phenylbutyl) - bicyclo-[3.1.0]hexane-3-one (Formula XLIV).

b. A solution of the Formula-XLIV dihydroxy compound above (about 8.0 g.) and 700 mg. of potassium bisulfate in 140 ml. of acetone is stirred at 25°C. for 64 hrs. Then, sodium carbonate monohydrate (710 mg.) is added, and the mixture is stirred 10 minutes. The acetone is evaporated at reduced pressure, and water is added. The aqueous solution is extracted repeatedly with dichloromethane, and the extracts are combined, washed with water, dried, and evaporated to give about 9.3 g. of an oil. The oil is chromatographed on 400 g. of silica gel, being eluted with 2 l. of 10% ethyl acetate in Skellysolve B, and then with 4 l. of 15% ethyl acetate in Skellysolve B. The 15% ethyl acetate eluates are evaporated to give about 7.4 g. of the Formula-XXIX compound, *endo* - 6 - (1,2 - dihydroxy - 4 - phenylbutyl) - bicyclo[3.1.0]hexan - 3 - one acetonide (Formula XXIX).

Preparation 7

Methyl 9 - Bromo - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 7 - nonynoate. (Formula XLVII: C_jH_{2j} aud C_pH_{2p} are valence bonds in meta relationship, C_qH_{2q} is methyl, Hal is bromo, R_2 is hydrogen and R_{10} is methyl).

a. To a cold, stirred solution of *m*-vinylanisole (13.4 g.) in 40 ml. of diethyl ether is slowly added a solution of bromine (15.9 g.) in 60 ml. of diethyl ether. The ether solution is used directly in converting the product, *m*-(1,2-dibromoethyl) anisole to *m*-methoxyphenylacetylene by dehydrohalogenation (see T. H. Vaughn, J. Am. Chem. Soc. 56, 2064, 1934). The ether solution above is slowly added, with vigorous stirring, t a mixture of sodium amide prepared from sodium (4.6 g.) in about 200 ml. of liquid ammonia. When the reaction is complete, the volume is reduced about one-half, and an equal volume of water is cautiously added. A layer

containing the product is separated, washed with dilute hydrochloric acid, dried, and distilled.

b. To a solution of the methoxy compound from a above in 250 ml. of dichloromethane, maintained at 0° C under nitrogen, is added dropwise over about a 1-hour period with vigorous stirring a solution of about 15 ml. of boron tribromide in 200 ml. of dichloromethane. Cooling and stirring continue for one hr. When the reaction is complete as shown by TLC, there is added cautiously a solution of sodium carbonate in water to neutralize the mixture. Thereafter, the solution is saturated with sodium chloride (added as a solid), and the organic phase is separated and combined with additional ethyl acetate washings of the aqueous phase. The organic solutions are washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to yield the acetylenic phenol.

c. To the acetylenic phenol (step b, 11.8 g.), is added gradually a solution of sodium ethoxide (prepared from sodium and absolute ethanol). Thereafter, ethylene chlorohydrin (8.0 g.) is added in small portions. When all has been added, the mixture is heated at reflux for about one hr. or until completion, then filtered hot. The combined filtrate and ethanol washings are concentrated to remove alcohol, and the product distilled under reduced pressure.

To the hydroxyethyl ether (16.2 g.) as obtained above, cooled to 15—20°C., is added 20 ml. of dihydropyran and 100 ml. of diethylether, and, with stirring, 1 ml. of anhydrous diethyl ether saturated with hydrogen chloride. After the exothermic reaction has diminished, the mixture is kept at 25° C. for 15 hours. The mixture is washed with aqueous sodium bicarbonate, water, and dried then concentrated under reduced pressure to yield the tetrahydropyranyl ether.

d and e. To a solution of the above tetrahydropyranyl ether of the substituted acetylene (10 g.) in anhydrous tetrahydrofuran (180 ml.) at −78° C. under argon is added the equivalent molecular amount of n-butyllithium in hexane. The resulting solution is stirred at −78° C. for an additional 30 minutes. A suspension of dry paraformaldehyde (two equivalents) in anhydrous tetrahydrofuran is added and the mixture warmed to room temperature over a 30-min. period. It is stirred an additional 1 hour and poured into saturated sodium chloride solution, then extracted with ether and dried to yield the hydroxy compound.

f. The hydroxy compound of step e is converted to the bromo compound by first forming the mesyl derivative by reaction with methanesulfonyl chloride (4 ml.) in pyridine (80 ml.) at −20° C. The mixture is stirred one hour at −20° C., and then is poured into a stirred mixture of 3 normal hydrochloric acid (300 ml.) and ice water (500 ml.). This mixture is extracted with diethyl ether, the extract is washed with cold one normal hydrochloric acid and brine, then dried and concentrated. To a solution of the residue (mesyl derivative) in dry acetone (100 ml.) is added lithium bromide (5 g.) and the mixture stirred and heated at reflux one hour, then kept at 25° C. for 15 hours. The acetone is evaporated under reduced pressure, and the residue is extracted with diethyl ether. The extract is washed with water and brine, then dried and concentrated. The residue is chromatographed on silica gel, eluting with 10% ethyl acetate in Skellysolve B. Fractions shown by TLC to contain the product are combined and evaporated to give the Formula-LIII intermediate.

g. The product of step f above is converted to the corresponding carboxylic acid and its methyl ester as follows. The tetrahydropyranyloxy group is replaced by hydroxyl by contacting the product of f with a mixture of acetic acid/water/tetrahydrofuran (20/10/3) at 40° C. for 2 hours, thereafter removing solvents under reduced pressure.

The substituted glycol from above is oxidized to the acid in acetone solution, using a slight excess of Jones reagent (21 g. chromic anhydride/60 ml. water/17 ml. conc. sulfuric acid) while cooling to maintain a temperature of −5 to 0° C. After about 60 min., isopropyl alcohol is added, the mixture is stirred for 10 min., and then poured into ice water. The acid product is isolated by extraction with chloroform, drying over sodium sulfate, and concentration under reduced pressure.

The acid from above is converted to the methyl ester by reaction with diazomethane in diethyl ether at about 10—25° C., followed by evaporation to yield the desired Formula-XLVII title compound.

Following the procedures of Preparation 7, but replacing *m*-vinylanisole with methyl (*o*, *m*, or *p*-) vinylbenzyl ether, there are obtained, respectively, methyl 9-bromo - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - 7 - nonynoate, methyl 10 - bromo - 3 - oxa - 4,8 - *inter* - *m* - phenylene - 5,6,7 - trinor - 8 - decynoate, and methyl 11 - bromo - 3 - oxa - 4,9 - *inter* - *p* - phenylene - 5,6,7,8 - tetranor - 9-undecynoate.

Preparation 8

Methyl 9 - Bromo - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *cis* - 7 - nonenoate (Formula XLVIII: C_jH_{2j} and C_pH_{2p} are valence bonds in meta relationships. C_qH_{2q} is methylene, Hal is bromo, R_2 is hydrogen and R_{10} is methyl).

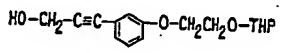
A solution of methyl 9 - bromo - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-7-nonynoate (2.0 g., Preparation 7) in 10 ml. of pyridine is hydrogenated in the presence of a 5% palladium on barium sulfate catalyst (150 mg.) at 25° C. and one atmosphere. The resulting mixture is filtered and evaporated to about one-third the original volume. Four volumes of ethyl acetate is added, and the remaining pyridine is removed by addition of ice and one N hydrochloric acid. The ethyl acetate layer is separated, washed successively with one N hydrochloric acid and brine, dried, and evaporated. The residue is chromatographed on 250 g. of silica gel which has previously been acid-washed to pH 4 (Silicar CC_4, 100—200 mesh, Mallincrodt—Registered Trade Mark—Co.), eluting with 3 l. of 25—75% ethyl acetate-Skellysolve B gradient, collecting 100-ml. fractions. The fractions shown to have the desired product free of starting material by TLC are combined and evaporated under reduced pressure to give the desired Formula-XLVIII title compound containing the *cis* —CH=CH radical.

Following the procedures of Preparation 8, but replacing methyl 9-bromo-3-oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 7 - nonynoate with methyl 9 - bromo - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - 7 - nonynoate, methyl 10 - bromo - 3 - oxa - 4,8 - *inter* - *m* - phenylene - 5,6,7 - trinor - 8 - decynoate, or methyl 11 - bromo - 3 - oxa - 4,9 - *inter* - *p* - phenylene - 5,6,7,8 - tetranor - 9 - undecynoate (from the paragraphs following Preparation 7), there is obtained the corresponding Formula-XLVIII-enoate compounds in which *cis* —CH=CH— has replaced —C≡C—.

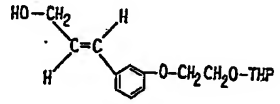
Preparation 9

Methyl 9 - Bromo - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *trans* - 7 - nonenoate. (Formula XLIX: C_jH_{2j} and C_pH_{2p} are valence bonds in meta relationship, C_qH_{2q} is methylene, Hal is bromo, R_2 is hydrogen and R_{10} is methyl).

A solution of the compound represented by the formula

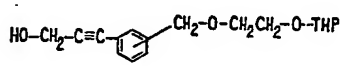


(1.0 g., Preparation 7, step e) in 20 ml. of tetrahydrofuran is cooled to −10° C. This solution is added to a fresh solution of lithium aluminium hydride (110% of theory) in tetrahydrofuran. The reaction mixture is stirred for 16 hours at 25° C. ambient temperature. Then, water (20 ml.) is added, and the resulting solution is acidified with one N hydrochloric acid, and then extracted with ethyl acetate. The extract is washed successively with aqueous sodium bicarbonate solution and brine, dried, and evaporated under reduced pressure. The residue is chromatographed on silica gel, eluting with a 25—75% ethyl acetate-Skellysolve B gradient, combining fractions shown to have the desired product by TLC, and removing solvent from those combined fractions under reduced pressure to yield a compound represented by the formula



Thereafter, following the procedures of Preparation 7, steps f through g, there is obtained the desired Formula-XLIX title compound containing the *trans* —CH=CH— moiety.

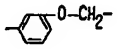
Following the procedures of Preparation 9, but replacing the compound having the formula



wherein the THP-terminated moiety is attached to the ring in ortho, meta, or para configuration, there is obtained the corresponding formula-XLIX compound in which trans —CH=CH— has replaced —C≡C—.

Example 1

Methyl 7 - [*Endo* - 6 - (1 - heptenyl) - 3 - oxobicyclo - [3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - heptanoate (Formula XXXVII, Chart E: G is n-pentyl; R_2, R_3, and R_4 are hydrogen; R_{10} is methyl; Z is



and ~ is alpha and *endo*).

A. A solution prepared from *endo* - 6 - (1 - heptenyl - 3 - (1 - pyrrolidinyl) - bicyclo[3.1.0]hex - 2 - ene (Preparation 1, 5.0 g.) and methyl[*m* - (chloromethyl) phenoxy]acetate (Preparation 2, 4.4 g.) in 60 ml. of dioxane is stirred under a nitrogen atmosphere at about 25° C for 2 days and then heated under reflux for 7 hrs. To the reaction mixture is added water. The solution is heated on a steam bath, cooled and extracted with ether. The extract is washed, first with dilute (about 5% hydrochloric acid, then brine, and dried and concentrated. The residue is chromatographed on 700 g. of silica gel prepared with 20% ether-isomeric hexane mixture (Skellysolve B) and eluted with 1.5 l. of 20% ether-Skellysolve B, 1.5 l. of 25% ether-Skellysolve B, and 1.5 l. of 30% ether-Skellysolve B, collecting 100-ml. fractions. Fractions 25—31 give the desired Formula-XXXVII title compound (1.7 g.).

B. Alternate synthesis.—A solution of potassium tert-butoxide (9.0 g.) in 500 ml. of nitrogen-purged tetrahydrofuran is added dropwise during 45 min. to a stirred solution of the Formula-XXXVI bicyclo olefin, *endo* - 6 - (1 - heptenyl)bicyclo [3.1.0]hexan - 3 - one (see Example 9 of West Germany Offenlegungsschrift No. 1,937,912, cited above) (10.0 g.), and methyl [*m*-(chloromethyl)phenoxy]acetate (Preparation 2, 13 g.) in 250 ml. of tetrahydrofuran under nitrogen at 25° C. The resulting mixture is acidified at once with 120 ml. of 5% hydrochloric acid, and then is concentrated under reduced pressure below 40° C to remove most of the tetrahydrofuran. Water (400 ml.) is added to the residue, and the mixture is extracted with three 400-ml. portions of ethyl acetate. The combined extracts are washed successively with aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution, dried, and evaporated under reduced pressure. The residue is chromatographed over 4 kg. of silica gel wet-packed with 20% ether-isomeric hexane mixture (Skellysolve B) and eluted with ether-Skellysolve B mixtures having 20—30% ether. Fractions shown by TLC to contain the desired alkylation product are combined to yield the Formula-XXXVII (Chart E) alkylated olefin title compound.

Following the procedure of Example 1-B but replacing the Formula-XXXVI (Chart E) *endo* - 6 - (1 - heptenyl)bicyclo[3.1.0]hexane - 3 - one with the corresponding bicyclo olefins prepared by reaction of the 3 - tetrahydropyran - 2 - yl ether of *endo* - bicyclo[3.1.0]hexan - 3 - ol - 6 - carboxaldehyde with intermediate quaternary phosphonium halides (see above-cited West Germany Offenlegungsschrift No. 1,937,912) prepared from 1-bromobutane, 1-chloropentane, 1-bromoheptane, and 1-chlorooctane, there are obtained the corresponding Formula-XXXVII alkylated olefin compounds wherein G is straight chain alkyl of 3, 4, 6, and 7 carbon atoms, respectively.

Also following the procedure of Example 1-B but employing instead Formula-XXXVI bicyclo olefins prepared from 1 - bromo - 2 - fluorobutane, 1 - chloro - 2 - fluoropentane, 1 - bromo - 2 - fluorohexane, 1 - bromo - 2 - fluoroheptane, and 1-chloro - 2 - fluorooctane, there are obtained the corresponding Formula-XXXVII alkylated olefin compounds wherein G is straight chain alkyl of 3 to 7 carbon atoms, inclusive, with a fluoro substituent at the 1-position.

Also following the procedure of Example 1-B but employing, instead, Formula-XXXVI bicyclo olefins prepared from primary bromides of the formula $X—(CH_2)_b—CH_2Br$, wherein b is one, 2, 3, or 4, and X is isobutyl, tert-butyl, 3,3-difluorobutyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, and 3,3,4,4,4-pentafluorobutyl, there are obtained compounds corresponding to the Formula-XXXVII product of Example 1-B with $X—(CH_2)_b—CH=CH—$ in place of the 1-heptenyl radical.

Also following the procedure of Example 1-B but employing, instead, Formula-XXXVI bicyclo olefins prepared from primary bromides of the formula

$$CH_3—(CH_2)_c—CR_{21}R_{22}—CH_2Br$$

wherein c is 2, 3, or 4, and R_{21} and R_{22} are methyl or ethyl, e.g.

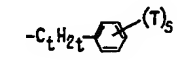
$CH_3—(CH_2)_2—C(C_2H_5)_2—CH_2Br$, $CH_3—(CH_2)_3—CH(CH_3)—CH_2—Br$,

$CH_3—(CH_2)_3—CH(C_2H_5)—CH_2—Cl$, $CH_3—(CH_2)_3—C(CH_3)_2—CH_2—Br$,

and $CH_3—(CH_2)_2—C(CH_3)(C_2H_5)—CH_2—Br$,

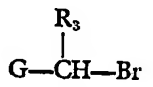
there are obtained the corresponding Formula-XXXVII alkylated olefin compounds wherein G is mono- or di-substituted at the 1-position with methyl or ethyl.

Also following the procedure of Example 1-B but employing, instead, Formula-XXXVI bicyclo olefins prepared from α-bromotoluene, (2-bromoethyl)benzene, (5-chloropentyl)benzene, (6-bromohexyl)benzene, and (7-iodoheptyl)benzene; from (1-chloroethyl)benzene, (1-bromopropyl)benzene, (2-bromopropyl)benzene, (3-chloropentyl)benzene, (4-bromopentyl)benzene, (6-bromononyl)benzene and (7-bromononyl) benzene; from 1-bromo-2-phenylpropane, 1-bromo-2-methyl-2-phenylpropane, 1-chloro - 2 - ethyl - 3 - phenylpropane, 1 - bromo - 2 - methyl - 4 - phenylbutane, and 1 - bromo - 2,2 - dimethyl - 5 - phenylpentane; from α - bromo - *m* - xylene, α - chloro - *p* - ethyltoluene, α - bromo - *p* - chlorotoluene, α′ - chloro - α,α,α - trifluoro - *m* - xylene, 1 - (2 - bromoethyl) - 4 - fluorobenzene, 1 - (5 - bromopentyl) - 2 - chlorobenzene, 4 - (3 - iodopropyl) - 1,2 - dimethoxybenzene, and 1 - (3 - bromohexyl) - 2,4,6 - trimethylbenzene; and from (2 - bromo - 1 - fluoroethyl)benzene, (2 - bromo - 1 - fluoropropyl)benzene, (2 - chloro - 1 - fluoro - 1 - methylpropyl) benzene, (5 - bromo - 4 - fluoropentyl)benzene, (7 - iodo - 6 - fluoropentyl)benzene, (4 - bromo - 3,3 - difluorobutyl)benzene, and (6 - bromo - 5,5 - difluorohexyl) benzene, there are obtained the corresponding Formula-XXXVII alkylated olefin compounds wherein G is

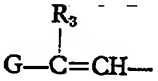


including compounds wherein C_tH_{2t} is substituted with one or 2 fluoro atoms.

Also following the procedure of Example 1-B, but using Formula-XXXVI bicyclo olefins obtained from the secondary bromides of the formula

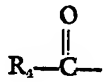


wherein G and R_3 are as defined above, R_3 being alkyl, there are obtained Formula-XXXVII alkylated olefins corresponding to the product of Example 1-B with

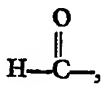


in place of the 1-heptenyl radical.

Also following the procedure of Example 1-B, but using Formula XXXVI bicyclo olefins obtained from bicyclo[3.1.0]hexane reactants with



in place of



a. There is first prepared the Formula-XXXVI olefin. Following the procedure for the Wittig synthesis in Examples 27, 28, and 29 of West Germany Offenlegungsschrift 1,937,912, cited above, but employing the tetrahydropyranloxy ether of *endo*-bicyclo[3.1.0]hexan - 3 - ol - 6 - carboxaldehyde and the Wittig ylide of 2 - chloroheptane, there is obtained *endo* - 6 - (2 - methyl - 1 - heptenyl) - 3 - oxobicyclo[3.1.0] hexan-3-one.

b. To a solution of the Formula-XXXVI olefin above (approximately 10.0 g.) in water is added a solution of potassium chlorate (10.0 g.) and osmium tetroxide (0.65 g.) in 250 ml. of water. The mixture is stirred vigorously for 5 hrs. at 50° C. Then, the cooled mixture is concentrated under reduced pressure, the residue is extracted repeatedly with dichloromethane, and the combined extracts are dried and evaporated. The residue is chromatographed on about 1000 g. of silica gel, and eluted successively with 3 l. of 10% ethyl acetate in a mixture of isomeric hexanes (Skellysolve B), with 5 l. of 25% ethyl acetate in Skellysolve B, and then with 50% ethyl acetate in Skellysolve B, collecting 500 ml. eluate fractions. Fractions shown by TLC to contain the desired product are combined and evaporated to dryness to give the Formula-XLIV product, *endo* - 6 - (1,2 - dihydroxy - 2 - methylheptyl) - bicyclo[3.1.0]hexan-3-one.

c. A solution of the Formula-XLIV dihydroxy compound above (about 8.0 g.) and 700 mg. of potassium bisulfate in 140 ml. of acetone is stirred at 25° C. for 64 hrs. Then, sodium carbonate monohydrate (710 mg.) is added, and the mixture is stirred 10 min. The acetone is evaporated at reduced pressure, and water is added. The aqueous solution is extracted respectedly with dichloromethane, and the extracts are combined, washed with water, dried, and evaporated. The residue is chromatographed on 400 g. of silica gel, being eluted with 2 l. of 10% etheyl acetate in Skellysolve B, and then with 4 l. of 15% ethyl acetate in Skellysolve B. The 15% ethyl acetate eluates are evaporated to give the Formula-XXIX ketal, *endo*-6-(1,2-dihydroxy-2-methylheptyl)-bicyclo[3.1.0]hexan-3-one acetonide.

d. To prepare the Formula-XXX compound (Chart D), the ketal above is alkylated following the procedure of Example 1-B, but using the Formula-XXIX ketal above instead of the Formula-XXXVI bicyclo olefin, and, replacing methyl [*m* - (chloromethyl)phenoxy]acetate with methyl 9 - chloro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *cis* - 7 - nonenoate (Preparation 8, above), thereby yielding the desired Formula-XXX title compound.

As shown in Chart D, the Formula-XXX alkylated ketal is transformed via the Formula-XXXI glycol, thence the mesylate, to a PGE-type compound. Concentrated hydrochloric acid (2.5 ml.) is added to a solution of the Formula-XXX product above (about 2.0 g.) in a mixture of 50 ml. of tetrahydrofuran and 2.5 ml. of water. The mixture is stirred at 25° C. under nitrogen for 6 hrs. The resulting mixture is then evaporated under reduced pressure, and the residue is extracted with ethyl acetate. The extract is washed with brine, dried, and evaporated to give methyl 9-[*endo*-6-(1,2 - dihydroxy - 2 - methylheptyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - cis - 7 - nonenoate (Formula XXXI). Thereafter, following the procedure of Example 3, there is obtained dl-15-methyl-3-oxa-3,7-*inter*-*m*-phenylene-4-nor-PGE_2 methyl ester.

Following the procedure of Example 9, but using Formula-XXXVI *exo* reactants in place of the *endo* reactant, there are obtained *exo* products in each intermediate and final step of Example 9.

With excess base (e.g., 26 g.) and a longer reaction time (e.g., 24 hrs. at 25° C.) during the alkylation step, the production of a substantial amount of the beta isomer is assured.

Following the procedures of Example 9-d, but using the *trans*-7-nonenoate of Preparation 9, above, instead of the *cis*-7-nonenoate, there is obtained the corresponding Formula-XXX alkylated ketal wherein the carboxy side chain is in *trans* configuration instead of *cis*.

Also following the procedures of Example 9, but replacing the Formula-XXXVI olefine with each of the *endo* and *exo* forms of the Formula-XXXVI bicyclo olefins described in the paragraphs following Example 1, there are obtained the corresponding alpha and beta, *exo* and *endo*, alkylated ketals within the scope of Formula XXX.

Also following the procedures of Example 9-d, but replacing methyl 9-chloro-3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *cis* - 7 - nonenoate with the Formula-XLVIII compounds of the paragraphs following Preparations 8 and 9, viz. *cis* or *trans* methyl 9 - bromo - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - 7 - nonenoate, methyl 10 - bromo - 3 - oxa - 4,8 - *inter* - *m* - phenylene - 5,6,7 - trinor - 8 - decenoate, and methyl 11 - bromo - 3 - oxa - 4,9 - *inter* - *p* - phenylene -

heptanoate, as a mixture of its isomers (Example 6, 2.8 g.) in dry tetrahydrofuran (150 ml.) at 50° C. is added 0.15 g. of osmium tetroxide followed by 2.8 g. of potassium chlorate in 60 ml. of water. The mixture is stirred vigorously at 50° C. for about 1.5 hrs. and is then concentrated under vacuum. The residue is extracted with dichloromethane. The extract is washed with water and brine, and then finally dried and concentrated under vacuum. The residue is chromatographed on a column prepared by wet-packing 500 g. of silica gel (E. Merck) with 1 liter of 50% ethyl acetate in Skellysolve B and 5 ml. of absolute ethanol. The column is eluted with 1 l. of 50% ethyl acetate in Skellysolve B and then gradient eluted with 4 l. of 50—75% ethyl acetate in Skellysolve B. Fractions of 100 ml. each are combined on the basis of TLC data. From fractions 12—29 there is obtained 2.6 g. of the desired Formula-XXXVIII title compound.

Example 8

dl - 3 - Oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - PGE_1 Ethyl Ester and dl - 15 - Beta - 3 - oxa - 4,7 - inter - *o* - phenylene - 5,6 - dinor - PGE_1 Ethyl Ester (Formula XIII: C_gH_{2g} is a valence bond; C_pH_{2p} and C_vH_{2v} are methylene; C_gH_{2g} and C_pH_{2p} are in ortho relationship; B is n-pentyl; the side-chain hydroxyl is in either natural (α) or epi (β) configuration; R_1 is ethyl; R_2, R_3, and R_4 are hydrogen; and $\sim$ is alpha).

Refer to Chart E. The Formula-XXXIX bismesylate is first prepared as follows. To a mixture of dl - ethyl 7 - [*endo* - 6 - (1,2 - dihydroxyhepthyl) - 3 - oxobicyclo [3.1.0]hex - 2α - yl] - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - heptanoate (Example 7, 2,6 g.) and 30 ml. of dry pyridine at 0° C. is added, with stirring, 2.7 ml. of methanesulfonyl chloride over a one-minute period. The mixture is stirred at 0° C. for 2.5 hrs., then cooled to about —10° C. and diluted with 2 ml. of water added dropwise over a 5-minutes period. Ice (20 g.) is added, and, after stirring the mixture for 5 min., about 150 ml. of ether-dichloromethane (3 : 1) is added. The organic solution was washed successively with dilute hydrochloric acid, water, dilute sodium bicarbonate solution, and brine, and finally dried and concentrated under vacuum to yield a mixture of the mesylates.

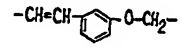
The residue of mesylates is converted to the PGE-type product by contacting with a mixture of acetone (100 ml.) and water (50 ml.) at about 25° C. for 16 hrs. Additional water (100 ml.) is added and the mixture concentrated under vacuum to remove acetone. The residue is extracted with a mixture of ether-dichloromethane (3 : 1) and the organic extract is washed with dilute sodium bicarbonate solution and brine, then dried and concentrated under vacuum. The residue (2.5 g.) is chromatographed on a column prepared by wet-packing 500 g. of silica gel (E. Merck) with one liter of ethyl acetate and 5 ml. of absolute ethanol. The column is eluted with 2.6 liters of ethyl acetate, then 400 ml. of 2% ethanol in ethyl acetate, then 500 ml. of 4% ethanol in ethyl acetate and finally with 2 liters of 10% ethanol in ethyl acetate, collecting fractions of 100 ml. Fractions are combined on the basis of TLC data.

From fractions 8—14 is obtained 350 mg. of the desired Formula-XIII 15-β PGE_1 title compound. This material has $\lambda_{max.}$ 279 mμ (ε 19,400) in alcoholic potassium hydroxide; key absorptions in the NMR spectrum at about 7.2 (apparent singlet), 5.25—5.48 (multiplet), 4.58 (singlet), 4.06 singlet, and 4.0—4.35 (quartet) δ; and mass spectral peaks at 414, 396, 310, and 292.

From fractions 18—37 is obtained 496 mg. of the desired Formula-XIII PGE_1 title compound. This material has $\lambda_{max.}$ 279 mμ (ε 21,750) in alcoholic potassium hydroxide; key absorptions in the NMR spectrum at about 7.18 (apparent singlet), 5.25—5.41 (multiplet), 4.58 (singlet), 4.02 (singlet), and 3.99—4.34 (quartet) δ; and mass spectral peaks at 414, 396, 310, and 292.

Example 9

Methyl 9 - [*Endo* - 6 - (1,2 - dihydroxy - 2 - methylheptyl) - 3 - oxobicyclo[3.1.0] hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *cis* - 7-nonenoate Acetonide (Formula XXX, Chart D: G is n-pentyl; J is *cis*-



R_2 and R_4 are hydrogen; R_3, R_{10}, R_{11}, and R_{12} are methyl; and $\sim$ is *endo* and alpha).

Refer to the sequence of reactions from Formula XLIII to Formula XXIX, and to Chart D.

Example 5

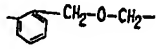
dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-PGA_1 (Formula XXI: C_gH_{2g} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-C_5H_{11}; R_1, R_2, R_3, and R_4 are hydrogen; and ~ is alpha).

Refer to Chart A. A solution of dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 methyl ester (Example 3, 300 mg.), 4 ml. of tetrahydrofuran and 4 ml. of 0.5 N hydrochloric acid is left standing at 25° for five days. Brine solution and dichloromethane-ether (1:3) are added and the mixture is stirred. The organic layer is separated, dried and concentrated. The residue is dissolved in ether which is washed with saturated aqueous sodium bicarbonate, dried and concentrated. The aqueous phase is quickly acidified with hydrochloric acid and extracted with dichloromethane which in turn is dried and concentrated. The residue is again dissolved in ether, extracted with aqueous sodium bicarbonate, and the aqueous phase is worked up as reported above. This procedure is repeated one additional time to yield the desired Formula-XXI title compound (120 mg.). This material has mass spectral peaks at 372, 354, 189, and 185; and λmax., in ethanol, 215 mμ (ε 12,400), 272 (ε 2250) and 278 (ε 2150).

Following the procedure of Example 5, the Formula XIII-to-XVI PGE compounds in their various spatial configurations described after Example 3 are transformed to the corresponding Formula XXI-to-XXIV PGA compounds, either as esters or as free acids.

Example 6

Ethyl 7 - [*Endo* - 6 - (1 - heptenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - heptanoate (Formula XXXVII: G is n-pentyl; R_2, R_3, and R_4 are hydrogen; R_{10} is ethyl; Z is



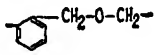
and ~ is alpha and *endo*).

The enamine of the Formula-XXXVI bicyclo-olefin is first prepared as follows. A mixture of endo - 6 - (*cis*- and *trans* - 1 - heptenyl) - bicyclo[3.1.0]hexan - 3 - one (10 g.), benzene (200 ml.), and pyrrolidine (15 ml.) is heated at reflux under a Dean-Stark water trap for 2 hrs. Thereafter about 140 ml. of distillate is taken off over a period of about 30 min. To the remaining liquid is added 100 ml. of toluene and the mixture is concentrated on a rotating evaporator under vacuum. A second portion of toluene (50 ml.) is added, and the mixture evaporated to give the enamine residue.

The above enamine, together with ethyl[*o* - (bromomethyl) - benzyloxy)]acetate (Preparation 3 above, 15 g.), and dry tetrahydrofuran (200 ml.) is heated at reflux for 4 hrs. and thereafter stirred at about 25° C. for 16 hrs. Water (25 ml.) is added and the mixture heated for 20 min. on a steam bath. Thereafter the volatiles are removed under vacuum, the residue is diluted with ether, and the organic solution is washed successively with dilute acid, water, dilute base, water, and brine, and finally dried and concentrated under vacuum. The residue is chromatographed on a column prepared by wet-packing 1300 g. of silica gel (E. Merck) with 2.5 l. of 25% diethyl ether in Skellysolve B and 13 ml. of absolute ethanol. The column is eluted with 2 l. of 25% ether in Skellysolve B and then gradient-eluted with 8 l. of 25—50% ether-Skellysolve B. Fractions of about 200 ml. are combined on the basis of TLC data. From fractions 24—31 there is obtained 2.9 g. of the desired Formula-XXXVII title compound as a mixture of *cis* and *trans* forms. This material has key absorptions in its NMR spectrum at about 7.21 (apparent singlet), 5.38—5.8 (multiplet), 4.62 (singlet), 4.06 (singlet), and 4.0—4.35 (quartet) δ. It has mass spectral 398 and 294.

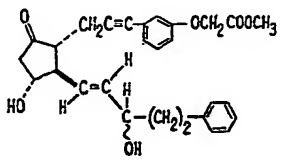
Example 7

Ethyl 7 - [*endo* - 6 - (1,2 - dihydroxyheptyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - heptanoate (Formula XXXVIII: G′ is n-pentyl; R_2, R_3, and R_4 are hydrogen; R_{10} is ethyl; Z is



and ~ is alpha and endo).

Refer to Chart E. to a solution of dl - ethyl 7 - [*endo* - 6 - (1 - heptenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor -



Also following the procedure of Example 3, but replacing methanesulfonyl chloride with an alkanesulfonyl chloride or bromide or with an alkanesulfonic acid anhydride, wherein the alkane radical contains 2 to 5 carbon atoms, inclusive, there is obtained from each dihydroxy compound the corresponding bis(sulfonic acid) esters encompassed by Formula XXXIX.

In each of the above transformations in Example 3, the monosulfonic acid ester is also obtained as a by-product, which is reacted with additional alkanesulfonyl halide or alkanesulfonic acid anhydride to give the corresponding bis(sulfonic acid) ester and thence recycled back to additional Formula-XL product.

For satisfactory yields of the bis-sulfonic acid ester, R_{10} is not hydrogen. Those intermediate compounds in which R_{10} is haloethyl, e.g., β,β,β-trichloroethyl, are especially useful in the sequence of reactions leading to the acid form of the prostaglandin-like products. Each of the *exo* and *endo*, alpha and beta, saturated and unsaturated oxa-phenylene bis(alkanesulfonic acid) esters is transformed to the corresponding oxa-phenylene PGE type compound encompassed by Formula XL.

Example 4

dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ Methyl Ester and dl - 3 -Oxa - 3,7 - inter - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\beta}$ Methyl Ester (Formula XVII: C_eH_{2e} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1 is methyl; R_2, R_3, and R_4 are hydrogen; and $\sim$ is alpha for the carboxyl-containing radical and either alpha or beta for the ring hydroxyl).

Refer to Chart A. A solution of dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6-trinor-PGE_1 methyl ester (Example 3, 300 mg.), 20 ml. of tetrahydrofuran, 2.0 ml. of hexamethyldisilazane, and 0.15 ml. of trimethylsilyl chloride is stirred at 25° for 20 hrs. The reaction mixture is concentrated *in vacuo*, benzene is added, the solution concentrated and this procedure is repeated. The residue is dissolved in 10 ml. of methanol, cooled in an ice-methanol bath, and sodium borohydride (60 mg.) in 20 ml. of cold water is added dropwise. The methanol is removed and the aqueous phase is extracted with dichloromethane, and the resulting dichloromethane solution is dried and concentrated *in vacuo*. The residue is chromatographed on 45 g. of silica gel using 70 ml. of ethyl acetate and then a gradient of 0—8% methanol ethyl acetate as eluting solvent, collecting 10-ml. fractions. Fractions 22—36 are combined and concentrated to yield the desired Formula-XVII $PGF_{1\alpha}$ title compound (100 mg.); mass spectral peak for tris-trimethylsilyl derivative at 622. Fractions 37—42 are combined and concentrated to yield a residue which is chromatographed on a preparative silica gel plate using 5% methanol-methylene chloride as eluting solvent. From the plate is obtained the desired Formula-XVII $PGF_{1\beta}$ title compound (25 mg.); mass spectral peak for tris-trimethylsilyl derivative at 622.

Following the procedure of Example 4, dl - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6-dinor-PGE_1 ethyl ester (Example 8 hereinafter) is transformed to dl-3-oxa-4,7-*inter*-*o*-phenylene-5,6-dinor-$PGF_{1\alpha}$ and -$PGF_{1\beta}$ ethyl esters.

Also following the procedure of Example 4, dl - 5,6 - dehydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 18 - phenyl - 4,19,20 - trinor - PGE_2 methyl ester (follow-in gExample 3) is transformed to the corresponding $PGF_{2\alpha}$ and $PGF_{2\beta}$ type compounds.

Also following the procedure of Example 4, the alkyl ester and free acid forms of Formula-XVII-to-XX oxaphenylene PGF compounds in their various spatial configurations, e.g., the $PGF_{1\alpha}$, $PGF_{1\beta}$, $PGF_{2\alpha}$, $PGF_{2\beta}$ trans-5,6-dehydro-$PGF_{1\alpha}$ and -$PGF_{1\beta}$, 5,6-dehydro-$PGF_{2\alpha}$ and -$PGF_{2\beta}$, 13,14-dihydro-$PGF_{1\alpha}$ and -$PGF_{1\beta}$ type compounds and their 8-iso and 15-beta isomers, are prepared by reduction of the corresponding Formula-XIII-to-XVI PGE-type alkyl ester or free acid, including those described above after Example 3.

Also following the procedure of Example 2, each of the Formula-XXXVII *exo* and *endo*, alpha and beta, saturated and acetylenic bicyclo[3.1.0]hexane esters defined above after Example 1 is oxidized to mixtures of the corresponding isomeric Formula-XXXVIII dihydroxy compounds.

Example 3

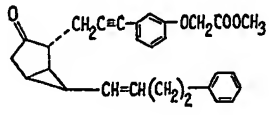
dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 Methyl Ester and dl - 15 - beta - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 Methyl Ester (Formula XIII: C_gH_{2g} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1 is methyl; R_2, R_3, and R_4 are hydrogen; and $\sim$ is alpha).

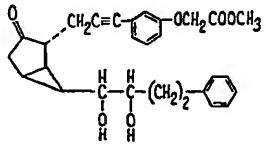
Refer to Chart E. To a solution of the Formula-XXXVIII dihydroxy compound, dl - methyl 7 - [*endo* - 6 - (1,2 - dihydroxyheptyl) - 3 - oxobicyclo[3.1.0] hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - heptanoate (800 mg. of a mixture of the slower and faster moving isomers of Example 2) in 10 ml. of pyridine, cooled to 0°, is added 1.2 ml. of methanesulfonyl chloride. The reaction mixture is stirred for 2 hrs. and 20 g. of ice is added. The mixture is extracted with ether-dichloromethane (1:1) and the organic layer is washed successively with dilute hydrochloride acid, water, saturated aqueous sodium bicarbonate, and brine, dried, and concentrated. The residue, containing the bismesylate, is treated with 15 ml. of acetone and 10 ml. of water and stirred for 8—16 hrs. at 25°. The acetone is removed in vacuo and the remaining solution is extracted with dichloromethane. The extract is dried and concentrated and the residue is chromatographed on 150 g. of silica gel using 500 ml. ethyl acetate followed by 3% methanol ethyl acetate as eluting solvent while collecting 30-ml. fractions. Fractions 15—24 are combined and concentrated to yield the desired Formula-XIII 15-β PGE_1 title compound (50 mg.); mass spectral peak at 404; ultraviolet absorption at 216 (ϵ=8100), 264 (ϵ=1100), 272 (ϵ=1600) and 278 (ϵ=1500) mμ. Fractions 26—35 are combined and concentrated to yield a residue which is re-chromatographed on 10 g. of silica gel using the same solvent system and collecting 1.5 ml. fractions. Fractions 22—29 are combined and concentrated to give the desired Formula-XIII PGE_1 title compound (75 mg.); mass spectral peak at 404; ultraviolet absorption at 216 (ϵ=7700), 264, 272 (ϵ=1500), and 278 (ϵ=1400) mμ.

Following the procedures of Example 3, each of the Formula-XXXVIII *endo*-1,2-dihydroxy oxa-phenylene esters following Example 2 is transformed to the corresponding *endo*-1,2-dimesyloxy oxa-phenylene ester, and thence to the corresponding PGE-type compound or its isomers.

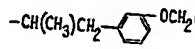
Also following the procedures of Example 3, each of the Formula-XXXVIII *exo*-1,2-dihydroxy oxa-phenylene esters corresponding to the above *endo*-1,2-dihydroxy esters is transformed to the corresponding *exo*-1,2-dimesyloxy ester, and thence to the corresponding PGE type compound or its isomers.

By the above-outlined procedures, following the steps of Chart E, there are obtained the specific PGE type esters represented by Figures XIII and XV, e.g. the esters of the oxa-phenylene PGE_1 compounds and 5,6-dehydro-PGE_2 compounds, including their 8-iso and 15-epi (β) forms. For example, dl-5,6-dehydro-3-oxa-3,7-*inter* - *m* - phenylene - 18 - phenyl - 4,19,20 - trinor - PGE_2 methyl ester and its 15 - epimer is obtained from dl - methyl 7 - [*endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6-trinor-7-nonynoate (Example 10 hereinafter) by way of the dihydroxy and bis(mesylate intermediates of Chart E, following Example 3, as represented by the following formulas:

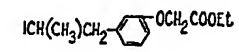




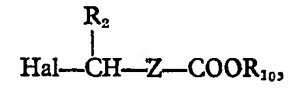
there are obtained *exo* and *endo*, alpha and beta, Formula-XXXVI alkylated bicyclo [3.1.0]hexanes each having a carboxylate-terminated side chain corresponding to one of the above specific omega-iodo alkylating agents. For example, the side chain will be alpha or beta



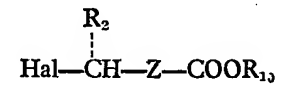
when the alkylating agent is



Also following the procedure of Example 1-B, but using in combination each of the alternative alkylating Formula-XLVI and -XLVII agents within the scope of



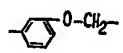
including the specific examples of those just mentioned, and each of the above-described Formula-XXXVI alternative bicyclo[3.1.0]hexane olefin reactants, there are obtained Formula-XXXVII *exo* and *endo*, alpha and beta, compounds corresponding to the products of Example 1-B, but different therefrom with respect to both the carboxylate-terminated side chain and the side chain attached to the cyclopropane ring of the product. In the same manner, alternative alkylating agents within the scope of



wherein R_{10} is other than ethyl, e.g., methyl, isopropyl, tert-butyl, octyl, cyclohexyl, benzyl, phenyl, and β,β,β-trichloroethyl are used.

Example 2

Methyl 7 - [*Endo* - 6 - (1,2 - dihydroxyheptyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - heptanoate (Formula XXXVIII, Chart E: G′ is n-pentyl; R_2, R_3, and R_4 are hydrogen; R_{10} is methyl; Z is



and $\sim$ is alpha and endo).

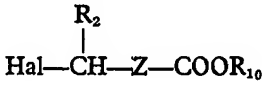
Refer to Chart E. To a solution of dl - methyl 7 - [*endo* - 6 - (1 - heptenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - inter - *m* - phenylene - 4,5,6 - trinor-heptanoate (Example 1, 1.7 g.) in 30 ml. of tetrahydrofuran at 50° is added with stirring osmium tetroxide (200 mg.) followed by potassium chlorate (1.2 g.) and 15 ml. of water. The reaction mixture is maintained at 50° for 2 hrs., cooled, the tetrahydrofuran is removed, and the aqueous phase is extracted with dichloromethane. The organic layer is dried and concentrated and the residue is chromatographed on 200 g. of silica gel. The column is eluted with 1 l. of 35% ethyl acetate-benzene and 1 l. of 40% ethyl acetate-benzene, collecting 30-mil. fractions. Fractions 26—30 contain one isomer (faster moving, less polar) of the desired Formula-XXXVIII title compound (350 mg.). Fractions 32—37 contain the other slower-moving (more polar) isomer (450 mg.). These materials show infrared spectral absorption at 3330 cm^{-1}.

Following the procedure of Example 2 but using the hex-2β-yl isomer in place of the hex-2α-yl isomer of the bicyclo reactant, methyl 7[*endo*-6-(1,2-dihydroxyheptyl) - 3 - oxobicyclo[3.1.0]hex - 2β - yl] - 3,7 - inter - m - phenylene - 4,5,6 - trinor-heptanoate is obtained.

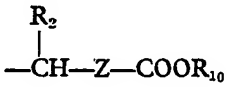
respectively. In the same manner, but using, according to Example 1-B, other esters of the above-described Formula-XLVI and -XLVII alkylating agents within the scope of R_{10} as above-defined, e.g., the isopropyl, tert-butyl, octyl, cyclohexyl, benzyl, and phenyl esters, there are obtained the corresponding Formula-XXXVII esters.

Also following the procedure of Example 1-B, but using in combination each of the above-described alternative Formula-XXXVI bicyclo olefins and each of the above-described alternative Formula-XLVI or -XLVII omega-halo alkylation agents, there are obtained Formula-XXXVII alkylated olefins corresponding to the product of Example 1-B but different therefrom with respect to both the carboxylate-terminated side chain and the side chain attached to the cyclopropane ring in the product.

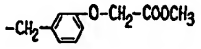
Also following the procedure of Example 1-B, but using in place of the Formula-XLVI halo alkylating agent of that Example, each of the other alkylating agents within the scope of



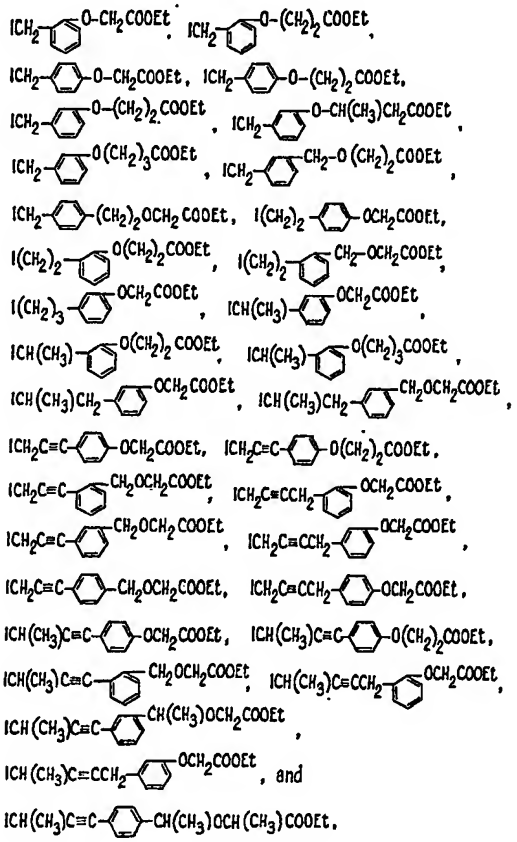
as above defined, i.e., alkylating agents of Formulas XLVI and XLVII as above-described, there are obtained alpha and beta *exo* and *endo* Formula-XXXVII compounds corresponding to the product of Example 1-B with each of the other



side chains in place of the

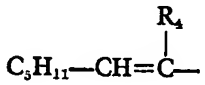


side chain of the Example 1-B product. For example, using as Formula-XLVI alkylating agents in the Example 1-B procedure, the following compounds wherein Et is ethyl;



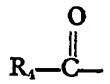
and

wherein R_4 is as defined above, there are obtained Formula-XXXVI alkylated olefins corresponding to the product of Example 1-B with

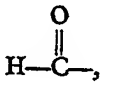


in place of the 1-heptenyl radical.

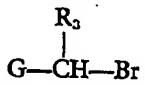
Also following the procedure of Example 1-B, but using Formula-XXXVI bicyclo olefins obtained from bicyclo[3.1.0]hexane reactants with



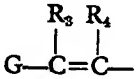
in place of



and primary and secondary bromides of the formula



(as above defined), there are obtained Formula-XXXVII alkylated olefins corresponding to the product of Example 1-B with

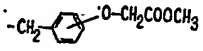


in place of the 1-heptenyl radical.

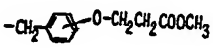
Also following the procedure of Example 1-B but using a larger amount of potassium tert-butoxide (16 g.) and maintaining the reaction mixture for 8 hrs. at 25° C. before addition of hydrochloric acid, a product is obtained which contains substantial amounts of both the above-described 2α-yl isomer and the corresponding 2β-yl isomer. These isomers are separated by the above-described silica gel chromatography.

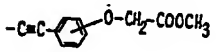
Also following the procedure of Example 1-B but using *exo* Formula-XXXVI bicyclo olefins in place of the *endo* reactant of Example 1-B, there are obtained the corresponding *exo* Formula-XXXVII alkylated olefins.

Also following the procedure of Example 1-B but replacing the methyl[*m*-(chloromethyl)phenoxy]acetate alkylating agent with the Formula-XLVI and -XLVII compounds, methyl 3 - [*m* - (chloromethyl)phenoxy]propionate, methyl 9 - bromo - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6, - trinor - 7 - nonynoate, and methyl 10 - bromo - 3 - oxa - 4,8 - *inter* - *m* - phenylene - 5,6,7 - trinor - 8 - decynoate, there are obtained alpha and beta, *exo* and *endo*, Formula-XXXVII alkylated olefins corresponding to the product of Example 1-B with

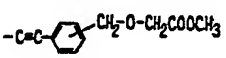


replaced with



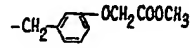


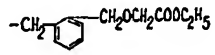
and

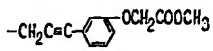


5,6,7,8 - tetranor - 9 - undecenoate, there are obtained the corresponding Formula-XXX compounds. Thereafter, these alkylated ketals are transformed following the steps of Chart D as described in Example 9 to the corresponding PGE_2 type compounds.

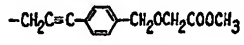
Also following the procedure of Example 9-d, but using in place of the nonenoate alkylating agent, methyl[*m*-(chloromethyl)phenoxy]acetate (Preparation 2), ethyl[*o*-(bromomethyl)benzyloxy]acetate (Preparation 3), methyl 9 - bromo 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 7 - nonynoate (Preparation 7), and methyl 11 - bromo - 3 - oxa - 4,9 - *inter* - *p* - phenylene - 5,6,7,8 - tetranor - 9 - undecynoate (following Preparation 7), there are obtained alpha and beta, *exo* and *endo*, compounds corresponding to the product of Example 9 with



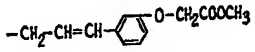




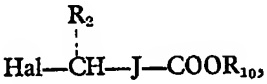
and



in place of the



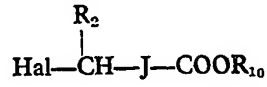
radical of the Example-9 Formula-XXX product. In the same manner, but using Formula-XLVI-to-XLIX alkylating agents within the scope of the formula



there are obtained the corresponding Formula-XXX products.

Also following Example 9-d, other esters of the nonenoate alkylating agent and of the other above-mentioned alkylating agents within the scope of R_{10} as above-defined, e.g., the methyl, isopropyl, tert-butyl, octyl, β,β,β-trichloroethyl, cyclohexyl, benzyl and phenyl esters, there are obtained the corresponding esters of these alpha and beta *exo* and *endo* Formula-XXX bicyclo[3.1.0]hexane cyclic ketal alkylation products.

Also following the procedure of Example 9 but using in combination each of the above-described alternative Formula-XXXVI bicyclo[3.1.0]hexane olefin reactants (e.g. following Example 1) and each of the above-described omega-halo alkylation reactants within the scope of



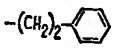
(e.g. following Example 1) there are obtained Formula-XXX compounds corresponding to the product of Example 9 but different therefrom with respect to both

the carboxylate-terminated side chain and the side chain attached to the cyclopropane ring of the product, and in their respective alpha or beta and *exo* or *endo* configuration.

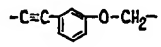
Following the procedure of Example 9 but using in place of the acetonide each of the specific Formula-XXX exo and endo, alpha and beta, saturated, *cis* and *trans* ethylenic, and acetylenic bicyclo[3.1.0]hexane cyclic ketal esters defined above, there are obtained the corresponding Formula-XXXI dihydroxy compounds, and thence the corresponding PGE type compounds.

Example 10

Methyl 7 - [*Endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 7 - nonynoate (Formula XXXVII, Chart E: G is



R_2, R_3, and R_4 are hydrogen; R_{10} is methyl; Z is

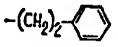


and ~ is *endo* and alpha).

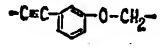
Refer to Chart E. Following the procedures of Example 1-B, but replacing *endo* - 6 - (1 - heptenyl)bicyclo[3.1.0]hexan - 3 - one with endo - 6 - (4 - phenyl - cis - 1 - butenyl) - bicyclo[3.1.0]hexan - 3 - one (Preparation 4), and replacing methyl [*m* - (chloromethyl)phenoxy]acetate with methyl 9 - chloro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 7 - nonynoate (Preparation 7), there is obtained the desired Formula-XXXVII title compound.

Example 11

Methyl 7 - [*Endo* - 6 - (4 - phenyl - 1,2 - dimesyloxybutyl) - 3 - oxobicyclo[3.1.0] hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor 7 - nonynoate (Formula XXXIX, Chart E: G′ is



R_2, R_3, and R_4 are hydrogen; R_{10} and R_{13} are methyl; Z is



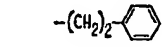
and ~ is alpha and *endo*).

a. There is first prepared the Formula-XXXVIII dihydroxy compound. Following the procedures of Example 2, but replacing dl - methyl 7 - [*endo* - 6 - (1 - heptenyl) - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - heptanoate with dl - methyl 7 - [*endo* - 6 - (4 - phenyl - cis - 1 - butenyl) - 3 - oxobicyclo[3.1.0] hex - 2α -yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor 7 - nonynoate (Example 10), there are obtained isomers of the desired Formula-XXXVIII compound, dl - methyl 7 - [*endo* - 6 - (4 - phenyl - 1,2 - dihydroxybutyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 7-nonynoate.

b. Following the procedures of Example 3, but replacing that Formula-XXXVIII dihydroxy heptanoate compound with the Formula-XXXVIII nonynoate compound of A above, there is obtained the desired Formula-XXXIX dimesyloxy title compound.

Example 12

Methyl 9 - [*Endo* - 6 - (1,2 - dihydroxy - 4 - phenylbutyl) - 3 - oxobicyclo[3.1.0] hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *trans* - 7-nonenoate Acetonide (Formula XXX, Chart D: G is



J is *trans*

R_2, R_3, and R_4 are hydrogen; R_{10}, R_{11}, and R_{12} are methyl; and ~ is *endo* and alpha).

Refer to the sequence of reactions from Formula XLIII to Formula XXIX, and to Chart D.

a. There is first prepared the Formula-XLIV dihydroxy compound. To a solution of the Formula-XXXVI olefin (Preparation 4, above, approximately 10.0 g.) in water is added a solution of potassium chlorate (10.0 g.) and osmium tetroxide (0.65 g.) in 250 ml. of water. The mixture is stirred vigorously for 5 hrs. at 50° C. Then, the cooled mixture is concentrated under reduced pressure, the residue is extracted repeatedly with dichloromethane, and the combined extracts are dried and evaporated. The residue is chromatographed on about 1000 g. of silica gel, and eluted successively with 3 l. of 10% ethyl acetate in a mixture of isomeric hexanes (Skellysolve B), with 5 l. of 25% ethyl acetate in Skellysolve B, and then with 50% ethyl acetate in Skellysolve B, collecting 500 ml. eluate fractions. Fractions shown by TLC to contain the desired product are combined and evaporated to dryness to give *endo*-6-(1,2-dihydroxy-4-phenylbutyl)-bicyclo[3.1.0]hexan-3-one (Formula XLIV).

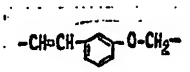
b. A solution of the Formula-XLIV dihydroxy compound above (about 8.0 g.) and 700 mg. of potassium bisulfate in 140 ml. of acetone is stirred at 25° C. for 64 hrs. Then, sodium carbonate monohydrate (710 mg.) is added, and the mixture is stirred 10 min. The acetone is evaporated at reduced pressure, and water is added. The aqueous solution is extracted repeatedly with dichloromethane, and the extracts are combined, washed with water, dried, and evaporated. The residue is chromatographed on 400 g. of silica gel, being eluted with 2 l. of 10% ethyl acetate in Skellysolve B, and then with 4 l. of 15% ethyl acetate in Skellysolve B. The 15% ethyl acetate eluates are evaporated to give the Formula-XXIX ketal, *endo*-6-(1,2-dihydroxy-4-phenylbutyl)-bicyclo[3.1.0]hexan-3-one acetonide.

c. To prepare the Formula-XXX compound, the ketal above is alkylated following the procedure of Example 1-B, but replacing methyl[*m*-(chloromethyl)phenoxy]acetate with methyl 9 - chloro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *trans* - 7 - nonenoate (Preparation 9, above), thereby yielding the desired Formula-XXX title compound.

Following the procedures of Example 9, the Formula-XXX compound is transformed via the Formula-XXXI and -XXXII compounds to the corresponding Formula-XXXIII PGE-type compound.

Example 13

9 - [*Endo* - 6 - (1,2 - dihydroxy - 2 - methylheptyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *cis* - 7 - nonenoic Acid Acetonide (Formula LXIV, Chart F: G is n-pentyl; J is *cis*



R_2 and R_4 are hydrogen; R_3, R_{11}; and R_{12} are methyl; and ~ is alpha and *endo*.

Refer to Chart F. A solution of sodium borohydride (1.5 g.) in 10 ml. of water is added with stirring to a solution of Formula-LX methyl 9 - [*endo* - 6 - (1,2 -

dihydroxy - 2 - methylheptyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *cis* - 7 - nonenoate acetonide (5.0 g.) in 110 ml. of absolute ethanol at 0° C. The mixture is stirred for 2.5 hrs. at 0° to 5° C. Then, 40 ml. of acetone is added, and, after 5 min., the mixture is evaporated under reduced pressure. The residue is extracted with dichloromethane, and the extract is washed successively with dilute hydrochloric acid and saturated aqueous sodium chloride solution, dried, and evaporated to give the Formula-LXI compound, methyl 9 - [*endo* - 6 - (1,2 - dihydroxy - 2 - methylheptyl) - 3 - hydroxybicyclo[3.1.0] hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *cis* - 7-nonenoate acetonide.

This Formula-LXI cyclic ketal hydroxy ester is dissolved in a mixture of methanol (100 ml.) and 45% aqueous potassium hydroxide solution (30 ml.), and the solution is stirred under nitrogen at 25° C. for 15 hrs. Two volumes of water are then added, and the mixture is acidified with cold hydrochloric acid and then extracted with a mixture of dichloromethane and diethyl ether (1:3). The extract is washed with saturated aqueous sodium chloride solution, dried, and evaporated to give the Formula-LXII compound, 9 - [*endo* - 6 - (1,2 - dihydroxy - 2 - methylheptyl) - 3 - hydroxybicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-*cis*-7-nonenoic acid acetonide.

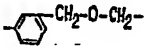
Jones reagent (7 ml.) is added to a solution of this Formula-LXII hydroxy acid in 120 ml. of acetone at 0° C. The mixture is stirred 5 min. at 0° C. Then, 5 volumes of water are added, and the mixture is extracted with a mixture of dichloromethane and diethyl ether (1:3). The extract is washed successively with dilute hydrochloric acid and saturated aqueous sodium chloride solution, dried, and evaporated to give the desired Formula-LXIV title compound.

Following the procedure of Example 13 but substituting for that Formula-LX compound, the Formula-LX compound of Example 12, viz. dl-methyl 9-[*endo*-6-(1,2 - dihydroxy - 4 - phenylbutyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *trans* - 7 - nonenoate acetonide, there is obtained the corresponding Formula LXI compound, methyl 9 - [*endo* - 6 - (1,2 - dihydroxy - 4 - phenylbutyl) - 3 - hydroxybicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *trans* - 7 - nonenoate; there is likewise obtained the corresponding Formula-LXII compound, 9 - [*endo* - 6 - (1,2 - dihydroxy - 4 - phenylbutyl) - 3 - hydroxybicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene -4,5,6 - trinor - *trans* - 7 - nonenoic acid; and there is likewise obtained the corresponding Formula-LXIV compound, 9 - [*endo* - 6 - (1,2 - dihydroxy - 4 - phenylbutyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter*-*m*-phenylene-4,5,6-trinor-*trans*-7-nonenoic acid acetonide.

Also following the procedure of Example 13, but using the specific Formula-XXX compounds described in and following Example 9 within the scope of Formula-LX, there are obtained the corresponding Formula-LXI, -LXII, and -LXIV compounds.

Example 14

7 - [*Endo* - 6 - (1 - heptenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - heptanoic Acid (Formula LXX, Chart G: G is n-pentyl; Z is



R_2, R_3, and R_4 are hydrogen; and ~ is alpha and *endo*).

Refer to Chart G. Following the procedure of Example 13, the Formula-LXVI compound, ethyl 7[*endo* - 6 - (1 - heptenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - heptanoate is reduced with sodium borohydride to the Formula-LXVII compound, ethyl 7 - [*endo* - 6 - (1 - heptenyl) - 3 - hydroxybicyclo[3.1.0]hex - 2α - yl - 3 - oxa - 4,7 - *inter* - *o* - phenylene-5,6-dinor)-heptanoate. That hydroxy ester is then saponified as described in Example 13 to the Formula-LXVIII compound, 7 - [*endo* - 6 - (1 - heptenyl) - 3 - hydroxybicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor-)heptanoic acid. That hydroxy acid is then oxidized as described in Example 13 to the desired Formula-LXX title compound.

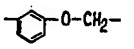
Following the procedure of Example 14 but substituting for that Formula-LXVI compound, the formula-LXVI compound of Example 10, viz. dl-methyl 7-[*endo*-6-(4-phenyl - *cis* - 1 - butenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 -

inter - *m* - phenylene - 4,5,6 - trinor - 7 - nonynoate, there is obtained on reduction the corresponding Formula-LXVII compound, methyl 7 - [*endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - 3 - hydroxybicyclo[3.1.0]hex - 2*α* - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 7 - nonynoate; there is likewise obtained on saponification the corresponding Formula-LXVIII compound, 7 - [*endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - 3 - hydroxybicyclo[3.1.0]hex - 2*α* - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 7 - nonynoic acid; and there is likewise obtained on oxidation the corresponding Formula-LXX compound, 7 - [*endo* - 6 - (4 - phenyl - *cis* - 1 - butenyl) - 3 - oxabicyclo[3.1.0]hex - 2*α* - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene-4,5,6-trinor-7-nonynoic acid.

Following the procedure of Example 14, but using in place of the Formula-LXVI 3-oxobicyclo[3.1.0]hexane ester, each of the specific Formula-LXVI *endo* and *exo*, alpha and beta, saturated and acetylenic esters described in and following the Examples 1, 6, and 10 is reduced with sodium borohydride to give the corresponding Formula-LXVII 3-hydroxy-bicyclo[3.1.0]hexane ester. That hydroxy ester is then saponified as described in Example 13 to the corresponding Formula-LXVIII 3-hydroxybicyclo[3.1.0]hexane acid. That hydroxy acid is then oxidized as described in Example 13 to the corresponding Formula-LXX 3-oxobicyclo[3.1.0]hexane acid.

Example 15

dl - 15 - Dehydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ Methyl Ester (Formula LXXV, Chart I: E is *trans* —CH=CH—, G is n-pentyl, J is



R_1 is methyl, R_2 is hydrogen, and ~ is alpha).

Refer to Chart I. A solution of dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-$PGF_{1\alpha}$ methyl ester (Example 4, about 0.5 g.) in 24 ml. of dioxane is stirred at 50° C. under nitrogen and 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone (0.37 g.) is added. The mixture is stirred at 50° C. for 24 hrs., cooled to room temperature, and filtered. The filter cake is washed with tetrahydrofuran, and the filtrate and wash are combined and concentrated under reduced pressure. The residue is taken up in dichloromethane and washed with brine, then dried over sodium sulfate and evaporated under reduced pressure. The residue is chromatographed over 90 g. of silica gel wet-packed in 8% ethanol in dichloromethane, eluting with 300 ml. of 2%, 300 ml. of 3%, 225 ml. of 7.5% and 245 ml. of 10% ethanol in dichloromethane, taking 15-ml. fractions. Fractions shown by TLC to contain the desired product are combined and evaporated to give the desired Formula-LXXV title compound.

Example 16

dl - 15 - Methyl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ Methyl Ester (Formula XVII: C_eH_{2e} and C_pH_{2p} are valence bonds in meta relationship, C_qH_{2q} is methylene, G is n-pentyl, R_1 and R_3 are methyl, R_2 and R_4 are hydrogen, and ~ is alpha).

Refer to Chart I. A solution of 0.413 g. of dl - 15 - dehydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ methyl ester (Example 15, about 0.4 g.), hexamethyldisilazane (3 ml.) and trimethylchlorosilane (0.5 ml.) in 20 ml.) of tetrahydrofuran is allowed to stand at about 25° C. for 20 hrs. The mixture is filtered and the filtrate is concentrated by evaporation under reduced pressure. Xylene (10 ml.) is added to the residue and removed by evaporation under reduced pressure. The residue is dissolved in anhydrous ether and 110% of the theoretical amount of 3 M methyl magnesium bromide in ether is added. The mixture is allowed to stand 20 min. at about 25° C. and poured into 100 ml. of saturated aqueous ammonium chloride. The ether layer is separated, the aqueous layer is extracted with ether, and the ether extracts are combined and washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The residue is dissolved in 300 ml. of ethanol and 30 ml. of water containing 3 drops of glacial acetic acid, and the mixture is stirred for 2 hrs. at about 25° C. The mixture is concentrated under reduced pressure to an aqueous residue and the residue is extracted with dichloromethane. The dichloromethane extract is evaporated under reduced pressure to give a residue which is chromatographed over 60 g. of silica gel wet-packed in 8% ethanol in dichloromethane, eluting with 200 ml. of 5% and 800 ml. of 10% ethanol in dichloro-

methane and taking 10-ml. fractions. Fractions shown by TLC to contain the desired product are combined and evaporated to yield the desired Formula-XVII title compound. Other fractions yield the 15-epimer.

Following the procedures of Examples 15 and 16, but using dl-3-oxa-3,7-*inter-m* - phenylene - 4,5,6 - trinor - $PGF_{1\beta}$ methyl ester instead of the $PGF_{1\alpha}$ compound, there is obtained first the 15-dehydro $PGF_{1\beta}$ compound, and finally the 15-methyl-3-oxa-3,7-*inter-m*-phenylene-4,5,6-trinor-$PGF_{1\beta}$ methyl ester, and its 15-epimer.

Likewise, using the corresponding 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor-$PGF_{1\alpha}$ or $PGF_{1\beta}$ compounds instead of the above oxa-phenylene compounds, there are obtained the corresponding 15-dehydro $PGF_{1\alpha}$ or $PGF_{1\beta}$-type compounds, and finally the 15 - methyl - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - $PGF_{1\alpha}$ or -$PGF_{1\beta}$ ethyl esters and their 15-epimers.

Example 17

dl - 13,14 - Dihydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 Methyl Ester (Formula XVI: C_tH_{2g} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1 is methyl; R_2, R_3, and R_4 are hydrogen; and $\sim$ is alpha).

Refer to Chart B. A solution of 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-PGE_1 methyl ester (Example 3, 100 mg.) in 10 ml. of ethyl acetate is shaken with hydrogen at about one atmosphere pressure at 25° C. In the presence of 5% rhodium on charcoal (15 mg.). After approximately one equivalent of hydrogen is absorbed, the hydrogenation is stopped, and the catalyst is removed by filtration. The filtrate is evaporated, and the residue is chromatographed on 25 g. of silica gel, eluting with 50—100% ethyl acetate gradient in Skellysolve B. Those fractions shown by TLC to contain the desired product free of the starting product and hydrogenation products are combined and evaporated to give the desired Formula-XVI title compound.

Following the procedure of Example 17, 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 methyl ester is reduced to 13,14 - dihydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE, ethyl ester. Likewise, 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - PGE_1 methyl ester is reduced to 13,14-dihydro - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - PGE_1 methyl ester.

Also following the procedure of Example 17, 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_2, -*trans* - 5,6 - dehydro - PGE_1, and -5,6 - dehydro - PGE_2 are each reduced to 13,14 - dihydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6-trinor-PGE_1, using two equivalents of hydrogen for the first two reactions, and three equivalents of hydrogen for the third. Likewise, the corresponding 3-oxa-4,7 - *inter* - *o* - phenylene - 5,6 - dinor - compounds are reduced to 3 - oxa - 4,7 - *inter-o*-phenylene-5,6-dinor-PGE_1.

Also following the procedure of Example 17, the ethyl ester and the free acid form of the Formula XIII-to-XV PGE compounds in their various spatial configurations are transformed to the corresponding 13,14-dihydro PGE_1 compound by catalytic hydrogenation, using equivalents of hydrogen appropriate to the degree of unsaturation of the reactant, i.e., one equivalent for the PGE_1 type, two equivalents for the PGE_2 type and *trans* - 5,6 - dehydro - PGE_1 type, and three equivalents for the 5,6-dehydro-PGE_2 type.

Also following the procedure of Example 17, 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ and its ethyl ester are reduced to 13,14 - dihydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - $PGF_{1\alpha}$ and its ethyl ester, respectively.

Also following the procedure of Example 17, the ethyl ester and the free acid form of the Formula XVII-to-XIX PGF compounds in their various spatial configurations are transformed to the corresponding 13,14 - dihydro $PGF_{1\alpha}$ or $PGF_{1\beta}$ compound by catalytic hydrogenation, using equivalents of hydrogen appropriate to the degree of unsaturation of the reactant.

Example 18

dl - 13,14 - Dihydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1 (Formula XXIV: C_tH_{2g} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1, R_2, R_3, and R_4 are hydrogen; and $\sim$ is alpha).

Refer to Chart B. A suspension of disodium azodiformate (50 mg.) in 5 ml. of absolute ethanol is added to a stirred solution of 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1 (Example 5, 50 mg.) in 10 ml. of absolute ethanol under nitrogen at 25° C. The mixture is made acid with glacial acetic acid, and then is

stirred under nitrogen at 25° C. for 8 hrs. The resulting mixture is evaporated under reduced pressure, and the residue is mixed with a mixture of diethyl ether and water (1:1). The diethyl ether layer is separated, dried, and evaporated to give the desired Formula-XXIV title product.

Following the procedure of Example 18, 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1 methyl ester is reduced to 13,14 - dihydro - 3 - oxa - 3,7 - *inter-m*-phenylene-4,5,6-trinor-PGA_1 methyl ester.

Also following the procedure of Example 18, 3 - oxa - 3,7 - *inter* - *m* - phenylene - PGA_2, *trans* - 5,6 - dehydro - PGA_1, and -5,6 - dehydro - PGA_2 are each reduced to 13,14 - dihydro - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1, using amounts of the disodium azodiformate reactant appropriate to the degree of unsaturation of the reactant.

Also following the procedure of Example 18, the methyl ester and the free acid form of the Formula XIII-to-XV PGE type compounds, the Formula XVII-to-IX PGF type compounds, the Formula XXI-to-XXIII PGA type compounds, and the Formula XXV-to-XXVII PGB type compounds are transformed to the corresponding 13,14-dihydro PGE_1, PGF_1, PGA_1, or PGB_1 type compound by diimide reduction, using amounts of disodium azodiformate reactant appropriate to the degree of unsaturation of the PGE, PGF, PGA, or PGB type reactant.

Example 19

dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1 Methyl Ester (Formula XXI: C_gH_{2g} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1 is methyl; R_2, R_3, and R_4 are hydrogen and ~ is alpha)

Refer to Chart D. A solution of the Formula-XXXII bismesylate, methyl 7-[*endo* - 6 - (1,2 - dimesyloxyheptyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - heptanoate (Example 3, about 10 g.) in 75 ml. of acetone is mixed with 10 ml. of water and 20 ml. of saturated aqueous sodium bicarbonate solution. The mixture is refluxed under nitrogen for 4 hrs. Then, the mixture is cooled, acidified with 5% hydrochloric acid, and extracted with ethyl acetate. The extract is washed with saturated aqueous sodium chloride solution, dried, and evaporated to give the desired Formula-XXXIV (-XXI) title product.

Following the procedure of Example 19, each of the bismesylates defined in Example 3 is transformed to the corresponding PGA-type ester, including the β,β,β-trichloroethyl esters. Thereafter, each of the β,β,β-trichloroethyl esters is transformed to the corresponding PGA-type free acid by the procedure of Example 23, below.

Example 20

dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGB_1 (Formula XXV: C_gH_{2g} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; and R_1, R_2, R_3, and R_4 are hydrogen).

Refer to Chart A. A solution of dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6-trinor-PGE_1 (200 mg.) in 100 ml. of 50% aqueous ethanol containing about one gram of potassium hydroxide is kept at 25° C. for 10 hrs. under nitrogen. Then, the solution is cooled to 10° C. and neutralized by addition of 3 N. hydrochloric acid at 10° C. The resulting solution is extracted repeatedly with ethyl acetate, and the combined ethyl acetate extracts are washed with water and then with brine, dried, and evaporated to give the desired Formula-XXV title compound.

Following the procedure of Example 20, 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6-trinor-PGA_1 is also transformed to the PGB_1-type title compound.

Following the procedure of Example 20, each of the Formula XIII-to-XVI PGE compounds and Formula XXI-to-XXIV PGA compounds are transformed to the corresponding PGB compounds.

Example 21

dl - 15 - Methyl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 Methyl Ester (Formula XIII: C_gH_{2g} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1 and R_3 are methyl; R_2 and R_4 are hydrogen; and ~ is alpha).

Refer to Chart H. A solution of dl - 15 - methyl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ methyl ester (95 mg.) in 40 ml. of acetone is cooled to −10° C. To it is added 110% of the theoretical amount of Jones reagent (in the proportions of 21 g. of chromic anhydride, 60 ml. of water, and 17 ml. of

concentrated sulfuric acid), pre-cooled to 0° C., with vigorous stirring. After about 10 min., isopropyl alcohol (1 ml.) is added to the cold reaction mixture. After 5 min., the mixture is filtered and the filtrate is concentrated at reduced pressure, and the residue is mixed with 5 ml. of brine. The mixture is extracted repeatedly with ethyl acetate, and the combined extracts are washed with brine, dried with anhydrous sodium sulfate, and concentrated at reduced pressure. The residue is chromatographed on 20 g. of neutral silica gel, eluting with 50% ethyl acetate in Skellysolve B. Evaporation of the eluates gives the desired Formula-XIII title product.

Following the procedure of Example 21, there is substituted for the dl-15-methyl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ methyl ester, the free acid, the propyl ester, the octyl ester, the cyclopentyl ester, the benzyl ester, the phenyl ester, the 2,4-dichlorophenyl ester, the 2-tolyl ester, or the β,β,β-trichloroethyl ester, there is obtained the corresponding dl - 15 - methyl - 3 - oxa - 3,7 - *inter*-*m*-phenylene-4,5,6-trinor-PGE_1 compound.

Following the procedure of Example 21, but substituting for the 15-methyl-3-oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ methyl ester, the methyl ester of each of the 15 - methyl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-$PGF_{1\beta}$, -$PGF_{2\alpha}$, -$PGF_{2\beta}$, -5,6-dehydro-$PGF_{2\alpha}$, -5,6-dehydro-$PGF_{2\beta}$, -dihydro-$PGF_{1\alpha}$, and -dihydro-$PGF_{1\beta}$ compounds in their various natural or 15-epi configurations and optical isomers is transformed to the corresponding PGE-type compound.

Following the procedure of Example 21, each of the various 15-alkyl-3-oxa-3,7-*inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ methyl ester compounds, including the 15-ethyl, 15-propyl, 15-butyl, and 15-substituted isomeric forms of propyl and butyl, is transformed to the corresponding PGE type compound.

Also following the procedure of Example 21, each of the 15-alkyl PGF-type acids and esters within the scope of Formula LXXII (Chart H) is transformed to a 15-alkyl PGE-type acid or ester encompassed by Formula LXXIII.

Example 22

dl - 15 - Methyl - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - PGA_1 Methyl Ester (Formula XXI: C_gH_{2g} is a valence bond; C_pH_{2p} and C_qH_{2q} are methylene; C_gH_{2g} and C_pH_{2p} are in ortho relationship; G is n-pentyl; R_1 and R_3 are methyl; R_2 and R_4 are hydrogen; and $\sim$ is alpha).

Refer to Chart J. A mixture of the Formula-LXXIX 15 - methyl - 3 - oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - PGE_1 methyl ester (6 mg.), dicyclohexylcarbodiimide (20 mg.), copper (II) chloride dihydrate (2 mg.), and diethyl ether (2 ml.) is stirred under nitrogen at 25° C. for 16 hrs. Then, additional dicyclohexylcarbodiimide (20 mg.) is added, and the mixture is stirred an additional 32 hrs. at 25° C. under nitrogen. The resulting mixture is filtered, and the filtrate is evaporated under reduced pressure. The residue is chromatographed by preparative thin layer chromatography with the A-IX system to give the desired Formula-XXI (-LXXX) product.

Following the procedure of Example 22, but substituting for the oxa-phenylene PGE_1 compound, the methyl esters of 15-methyl-3-oxa-4,7-*inter*-*o*-phenylene-5,6-dinor-PGE_2, -5,6-dehydro-PGE_2, and -dihydro-PGE_1, there are obtained the corresponding Formula-LXXX compounds, viz., the methyl esters of 15-methyl 3-oxa-4,7 - *inter* - *o* - phenylene - 5,6 - dinor - PGA_2, -5,6 - dehydro - PGA_2, and -dihydro-PGA_1.

Also following the procedure of Example 22, but substituting for the phenyl-substituted PGE_1 compound, the methyl esters of 15 - methyl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1, -PGE_2, -5,6 - dehydro - PGE_2, and -dihydro-PGE_1, there are obtained the corresponding Formula-LXXX compounds, viz., the methyl esters of 15 - methyl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-PGA_1, -PGA_2, -5,6-dehydro-PGA_2, and -dihydro-PGA_1.

Also following the procedure of Example 22, each of the Formula-LXXIX (Chart J) compounds defined above in Example 21 is transformed to the corresponding Formula-LXXX compound.

Example 23

dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 (Formula XIII: C_gH_{2g} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1, R_2, R_3, and R_4 are hydrogen; and $\sim$ is alpha).

Zinc dust (420 mg.) is added to a solution containing dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 β,β,β - trichloroethyl ester (100 mg.) in 5 ml. of a mixture of acetic acid and water (9:1 v/v). This mixture is stirred under

nitrogen 2 hrs. at 25° C. Ethyl acetate (4 volumes) is then added, followed by addition of 1 N. hydrochloric acid (one volume). The ethyl acetate later is separated, washed with water and then with brine, dried, and evaporated. The residue is chromatographed on 15 g. of acid-washed silica gel (Silicar CC4), being eluted with 100 ml. of 50%, 100 ml. of 80%, and 200 ml. of 100% ethyl acetate in Skellysolve B, collecting 20-ml. fractions. The fractions containing the desired product and no starting material or dehydration products as shown by TLC are combined and evaporated to give the desired Formula-XIII title compound.

Following the procedure of Example 23, each of the β,β,β-tribromoethyl, -triiodoethyl, β,β-dibromoethyl, -diiodoethyl, and the β-iodoethyl esters of 3-oxa-3,7-*inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 is converted to the free acid of 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 by reaction with zinc dust and acetic acid.

Following the procedure of Example 23, the β,β,β-trichloroethyl ester of dl-15-methyl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4 - nor - PGE_2 following Example 9 above is converted to the respective free acid compound using zinc dust with either propionic, butyric, pentanoic, or hexanoic acid instead of acetic acid.

Following the procedure of Example 23, the β,β,β-trichloroethyl ester of each of the PGE, PGF, PGA and PGB type compounds represented by Formulas XIII—XXVIII in their various structural configurations and optical isomers is treated with zinc dust and acetic acid to obtain the corresponding free acid form of the compound. The esters are prepared by the procedures disclosed herein, using as intermediates Formula-XXX cyclic ketals or Formula-XXXVII olefins wherein R_{10} is haloethyl, e.g., β,β,β-trichloroethyl. These intermediates are prepared either by alkylation of the respective Formula-XXIX cyclic ketal (Chart D) or Formula-XXXVI olefin (Chart E) with the appropriate alkylating agent wherein R_{10} is haloethyl, or by the transformation of the alkylated cyclic ketal or olefin by the steps shown in Charts F and G using procedures disclosed herein, yielding intermediates LXIII, LXV, LXIX, or LXXI.

Example 24

dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ and -$PGF_{1\beta}$ (Formula XVII: C_tH_{2t} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1, R_2, R_3, and R_4 are hydrogen; and ~ is alpha or beta).

A solution of 146 mg. of dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-$PGF_{1\alpha}$ ethyl ester in a mixture of 4.5 ml. of methanol and 1.5 ml. of water is cooled to 5° C. and 0.6 ml. of 45% aqueous potassium hydroxide is added. The mixture is allowed to stand 3.5 hrs. at 25° C., then is diluted with 75 ml. of water and extracted once with ethyl acetate to remove any neutral material. The aqueous layer is separated, made acid with dilute hydrochloric acid and extracted 4 times with ethyl acetate. The extracts are combined and washed 3 times with water, once with brine, dried over sodium sulfate, and evaporated to give the desired Formula-XVII $PGF_{1\alpha}$-type title compound.

Following the procedure of Example 24, the methyl ester of dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\beta}$ is transformed to the free acid, i.e. the Formula-XVII $PGF_{1\beta}$-type title compound.

Following the procedure of Example 24, the methyl or ethyl esters of the various oxa-phenylene PGF-type compounds and their isomers are transformed to the corresponding free-acid oxa-phenylene PGF-type compounds.

Example 25

dl - 3 - Oxa - 3,5 - *inter* - *m* - phenylene - 4 - nor - $PGF_{2\alpha}$ Methyl Ester (Formula XVIII: C_iH_{2i} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1 is methyl; R_2, R_3, R_4, R_5, and R_6 are hydrogen; and ~ is alpha).

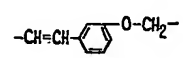
Refer to Chart C. dl - 5,6 - Dehydro - 3 - oxa - 3,5 - *inter* - *m* - phenylene - 4 - nor - $PGF_{2\alpha}$ methyl ester (200 mg.) in pyridine (4 ml.) and methanol (10 ml.) is hydrogenated in the presence of a 5%-palladium-on-barium sulfate catalyst (200 mg.) at 25° and atmospheric pressure. The reaction is terminated when slightly more than one equivalent of hydrogen is absorbed. The mixture is filtered and evaporated. Ethyl acetate is added and residual pyridine is removed by addition of ice and 3 N. hydrochloric acid. The ethyl acetate layer is washed with 1 N. hydrochloric acid and then with saturated aqueous sodium chloride solution, dried, and evaporated to yield the desired Formula-XVIII title product.

Following the procedure of Example 25, the 5,6-dehydro-oxa-phenylene PGF_2 compounds following Example 4 are reduced to the corresponding PGF_2 com-

pounds. Likewise, the 5,6-dehydro oxa-phenylene PGE, PGA, and PGB compounds disclosed herein are reduced to the corresponding PGE_2, PGA_2, and PGB_2 compounds.

Example 26

β,β,β - Trichloroethyl 9 - [*cndo* - 6 - (1,2 - dihydroxy - 2 - methylheptyl) - 3 - hydroxybicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - *cis* - 7 - nonenoate Acetonide (Formula LXIII, Chart F: G is n-pentyl; J is *cis*



haloethyl is β,β,β - trichloroethyl; R_2 and R_4 are hydrogen; R_3, R_{11}, and R_{12} are methyl; and $\sim$ is alpha and *endo*).

Refer to Chart F. Successively, β,β,β-trichloroethanol (25 ml.), pyridine (15 ml.), and N,N'-dicyclohexylcarbodiimide (4.0 g.) are added to a solution of Formula-LXII compound 9 - [*endo* - 6 - (1,2 - dihydroxy - 2 - methylheptyl) - 3 - hydroxybicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor-*cis*-7-nonenoic acid acetonide (Example 13, 2.0 g.) in 100 ml. of dichloromethane. This mixture is stirred 3 hrs. under nitrogen at 25° C. Water (50 ml.) is then added, and the mixture is stirred 10 min. The dichloromethane is evaporated under reduced pressure, and the residue is extracted repeatedly with ethyl acetate. The combined extracts are washed with ice-cold 3 N. hydrochloric acid. Then, the extracts are washed successively with aqueous sodium bicarbonate solution and brine, dried, and evaporated under reduced pressure. The residue is chromatographed on 600 g. of silica gel, eluting with 10 l. of a 20—100% ethyl acetate-Skellysolve B gradient, collecting 250-ml. fractions. The middle fractions which show the presence of a product on TLC are combined and evaporated under reduced pressure. The residue is chromatographed on 200 g. of silica gel impregnated with silver nitrate, eluting with 4 l. of a 20—100% ethyl acetate-Skellysolve B gradient, collecting 50-ml. fractions. The middle fractions which show a product free of starting materials on TLC are combined and evaporated under reduced pressure to give the Formula-LXIII title compound.

Following the procedure of Example 26, but using in place of the Formula-LXII 3-hydroxybicyclo[3.1.0]hexane acid acetonide, each of the specific *endo* and *exo*, alpha and beta, saturated and unsaturated Formula-LXII hydroxy acid ketals defined after Example 13, there are obtained the corresponding β,β,β-trichloroethyl esters of those 3-hydroxybicyclo[3.1.0]hexane acids.

Following the procedure of Example 26, but using in place of the Formula-LXII 3 - hydroxybicyclo[3.1.0]hexane acid ketal, each of the specific Formula-LXIV 3-oxo-acid ketals defined after Example 13, there are obtained the corresponding Formula-LXV β,β,β-trichloroethyl esters of those 3-oxo-acid ketals.

Following the procedure of Example 26 but using in place of the Formula-LXII 3-hydroxy-acid ketal, each of the specific Formula-LXVIII 3-hydroxy and Formula-LXX 3-oxo acids defined after Example 14, there are obtained the corresponding Formula-LXIX and Formula-LXXI β,β,β-trichloroethyl esters of those acids, respectively.

Following the procedures of Examples 9 and 3, each of the Formula-LXV cyclic ketal haloethyl esters of Example 26 is transformed to the corresponding Formula-XXXIII 3-oxa or 4-oxa phenyl-substituted PGE_1 β,β,β-trichloroethyl ester. Thence, following the procedure of Example 23, each of the esters is transformed to the oxa-phenylene PGE_1 acid compound wherein R_{10} of Formula XXXIII is replaced with hydrogen.

Following the procedure of Examples 2 and 3 each of the Formula-LXXI olefin haloethyl esters of Example 26 is transformed to the corresponding Formula-XL oxa-phenylene PGE_1 β,β,β-trichloroethyl ester. Thence, following the procedure of Example 23, each of the esters is transformed to the corresponding PGE_1-type acid compound wherein R_{10} of Formula XXXIII is replaced with hydrogen.

Example 27

dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1 Methyl Ester (Formula XXI: C_gH_{2g} and C_pH_{2p} are valence bonds in meta relationship; G is n-pentyl; R_1 is methyl; R_2, R_3, and R_4 are hydrogen; and $\sim$ is alpha).

A solution of diazomethane (about 50% excess) in diethyl ether (25 ml.) is added to a solution of dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1

(Example 5, 50 mg.) in 25 ml. of a mixture of methanol and diethyl ether (1 : 1). The mixture is allowed to stand at 25 C. for 5 min. Then, the mixture is evaporated to give the Formula-XXI title compound.

Following the procedure of Example 27, each of the other specific phenyl-substituted PGB type, PGA type, PGE type, and PGF type free acids defined above is converted to the corresponding methyl ester.

Also following the procedure of Example 27, but using in place of the diazomethane, diazoethane, diazobutane, 1-diazo-2-ethylhexane, and diazocyclohexane, there are obtained the corresponding ethyl, butyl, 2-ethylhexyl, and cyclohexyl esters of 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGA_1. In the same manner, each of the other specific phenyl-substituted PGB type, PGA type, PGE type, and PGF type free acids defined above is converted to the corresponding ethyl, butyl, 2-ethylhexyl, and cyclohexyl esters.

Example 28

dl-3-Oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor-PGE_1 Methyl Ester Diacetate.

Acetic anhydride (5 ml.) and pyridine (5 ml.) are mixed with dl-3-oxa-3,7-*inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 methyl ester (Example 3, 20 mg.), and the mixture is allowed to stand at 25° C. for 18 hrs. The mixture is then cooled to 0° C., diluted with 50 ml. of water, and acidified with 5% hydrochloric acid to pH 1. That mixture is extracted with ethyl acetate. The extract is washed successively with 5% hydrochloric acid, 5% aqueous sodium bicarbonate solution, water, and brine, dried and evaporated to give the title compound.

Following the procedure of Example 28 but replacing the acetic anhydride with propionic anhydride, isobutyric anhydride, and hexanoic acid anhydride, there are obtained the corresponding dipropionate, diisobutyrate and dihexanoate derivatives of dl-3-oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor-PGE_1 methyl ester.

Also following the procedure of Example 28, but replacing the 3-oxa-3,7-*inter*-*m* - phenylene - 4,5,6 - trinor - PGE_1 compound with 3 - oxa - 3,7 - *inter* - *m* - phenylene-4,5,6-trinor-$PGF_{1\alpha}$ and -$PGF_{1\beta}$, and 15-methyl-3-oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor-$PGF_{1\alpha}$ and -$PGF_{1\beta}$, there are obtained the corresponding triacetate derivatives of the 3-oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor-PGF cmpounds.

Also following the procedure of Example 28, each of the phenyl-substituted PGE type, PGF type, PGA type, and PGB type esters and free acids defined above is transformed to the corresponding acetates, propionates, isobutyrates, and hexanoates, the PGE-type derivatives being dicarboxyacylates, the PGF-type derivatives being tricarboxyacylates, and the PGA-type and PGB-type derivatives being monocarboxyacylates.

Example 29

dl-3-Oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor-PGE_1 Sodium Salt.

A solution of dl - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 (Example 23, in 100 mg.) in 50 ml. of a water-ethanol mixture (1 : 1) is cooled to 5° C. and neutralized with an equivalent amount of 0.1 N. aqueous sodium hydroxide solution. The neutral solution is evaporated to give the title compound.

Following the procedure of Example 29 but using potassium hydroxide, calcium hydroxide, tetramethylammonium hydroxide, and benzyltrimethylammonium hydroxide in place of sodium hydroxide, there are obtained the corresponding salts of dl-3-oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor-PGE_1.

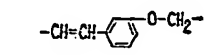
Also following the procedure of Example 29 each of the phenyl-substituted PGE type, PGF type, PGA type, and PGB type acids defined above is transformed to the sodium, potassium, calcium, tetramethylammonium, and benzyltrimethylammonium salts.

The various Preparations and Examples given above describe the preparation of racemic intermediates and final products. Each of the intermediates and final products named and defined above is also obtained in each of the enantiomeric forms, d and l, by resolution of that compound or by resolution of an intermediate used to prepare that compound. For example, d - 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6-trinor-PGA_1 free acid is prepared by resolution of dl-3-oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor-PGA_1 free acid (Example 5) or by dehydration as in Example 5 of optically active 3 - oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 free acid with the same absolute configuration. These resolutions are carried out by procedures known in the art, and may be used to obtain prostaglandin-like materials having the spatial configuration of the natural prostaglandins, as typified by the following Example.

Example 30

Natural Configuration 3 - oxa - 3,5 - *inter* - *m* - phenylene - 4- nor -PGE_2 and -$PGF_{2\alpha}$ Methyl Esters (Formula XIV and XVIII: wherein C_jH_{2j} and C_pH_{2p} are valence bonds in meta relationship; C_qH_{2q} is methylene; G is n-pentyl; R_1 is methyl; R_2, R_3, R_4, R_5, and R_6 are hydrogen; and ~ is alpha).

The process shown in Chart D is used to prepare the PGE_2-type compound first. The Formula-XXX cyclic ketal intermediate wherein G is n-pentyl; J is



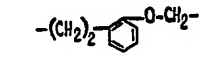
R_2, R_3, and R_4 are hydrogen; R_{10}, R_{11}, and R_{12} are methyl; and ~ is *endo* and alpha is prepared following the procedures of Example 9.

The Formula-XXX compound is resolved as its optical isomers by the method of Corey et al., J. Am. Chem. Soc. 84, 2938 (1962), by reacting this keto compound with optically active L(+)-2,3-butanedithiol in the presence of *p*-toluene-sulfonic-acid. The diastereomeric ketals are completely resolved on a preparative chromatographic column, and are then hydrolyzed separately, following the procedure of Example 9, to the Formula-XXXI dihydroxy compounds. Transformation to the Formula-XIV PGE_2-type compounds is accomplished by the procedures of Example 3. Of the separate diastereoisomers, one corresponds to the configuration of natural PGE_2 and the other to its enantiomer. Conversion of the PGE-type compound having the configuration of the natural product to the $PGF_{2\alpha}$-type methyl ester is done by borohydride reduction following the procedure of Example 4. The natural configuration-$PGF_{2\alpha}$-type free acid is formed from the methyl ester by saponification, following the procedure of Example 24.

Example 31

Natural Configuration 3 - Oxa - 3,5 - *inter* - *o* - phenylene - 4 - nor - PGE_1 Methyl Ester (Formula XIII: C_gH_{2g} is ethylene; C_pH_{2p} is a valence bond in ortho relationship to C_gH_{2g}; C_qH_{2q} is methylene; G is n-pentyl; R_1 is methyl; R_2, R_3, and R_4 are hydrogen; and ~ is alpha). Refer to Chart C.

A. Methyl 7 - [*endo* - 6 - (1 - heptenyl - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,5 - *inter* - *o* - phenylene - 4 - nor - heptanoate (Formula XXXVII, Chart E: G is n-pentyl; R_2, R_3, and R_4 are hydrogen; R_{19} is methyl; Z is



and ~ is alpha and *endo*).

1. Methyl[*o* - (3 - hydroxypropyl)phenoxy]acetate. To a solution of potassium t-butoxide (11.2 g.) in 150 ml. of dry tetrahydrofuran at 0—5° C. is added with stirring 3 - (*o* - hydroxyphenyl)propanol (15.2 g.) followed in a few minutes by methyl bromoacetate (20 g.). The cooling bath is removed and the mixture is stirred at ambient temperature until the reaction mixture becomes essentially neutral. The mixture is concentrated in vacuo at 30° C. and the residue is shaken with ether and water. The organic layer is washed with dilute potassium hydroxide solution, water, brine, and is dried over sodium sulfate and then concentrated in vacuo. The residue is distilled in a high vacuum to afford methyl[*o*-(3-hydroxypropyl)phenoxy] acetate.

2. Methyl[*o* - (3 - chloropropyl)phenoxy]acetate. A mixture of methyl[*o* - (3 - hydroxypropyl)phenoxy]acetate (step A-1, 25 g.) and thionyl chloride (20 ml.) is heated to reflux for 1—2 hrs. The excess thionyl chloride is removed in vacuo and the residue is distilled in a high vacuum to afford methyl[*o*-(3-chloropropyl)phenoxy] acetate.

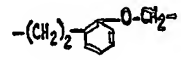
3. Methyl[*o* - (3 - iodopropyl)phenoxy]acetate. A mixture of methyl 2 - (3 - chloropropyl)phenoxyacetate (step A-2, 24.3 g.), acetone (250 ml.) and sodium iodide (30 g.) is heated to reflux with stirring for about 40 hrs. The mixture is

cooled, filtered and the filtrate is concentrated in vacuo at about 30° C. The residue is diluted with ether and the solution is washed with water, dilute sodium thiosulfate solution, brine and is dried over magnesium sulfate and then concentrated in vacuo. The product, methyl[*o*-(3-iodopropyl)phenoxy]acetate, is used directly in the next step.

4. Following the procedure of Example 1-B, but replacing the methyl[*m*-(chloromethyl)phenoxy]acetate with methyl[*o* - (3 - iodopropyl)phenoxy]acetate (step A-3, 18 g.) and allowing the alkylation reaction to proceed for about 5 min. before acidification with hydrochloric acid, there is obtained the desired Formula-XXXVII methyl 7 - [*endo* - 6 - (1 - heptenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,5-*inter-o*-phenylene-4-nor-heptanoate.

Following the procedure of Example 30, the above racemic Formula-XXXVII compound is resolved as two optically active isomers. These are both transformed by the subsequent steps of this example to the Formula-XIII PGE_1-type compounds, one of which corresponds to the configuration of natural PGE_1 and the other to its enantiomer.

B. Methyl 7 - [*endo* - 6 - (1,2 - dihydroxyheptyl) - 3 - oxo - bicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,5 - *inter* - *o* - phenylene - 4 - nor - heptanoate (Formula XXXVIII, Chart E: G′ is n-pentyl; R_2, R_3, and R_4 are hydrogen; R_{10} is methyl; Z is



and ~ is alpha and endo). To a solution of methyl 7 - [*endo* - 6 - (1 - heptenyl) - 3 - oxobicyclo[3.1.0]hex - 2α - yl] - 3 - oxa - 3,5 - *inter* - *o* - phenylene - 4 - nor - heptanoate (step A, above, 1.8 g.) in 30 ml. of tetrahydrofuran at 50° is added, with stirring osmium tetroxide (200 mg.) followed by potassium chlorate (1.2 g.) and 15 ml. of water. The reaction mixture is maintained at 50° for 2 hrs., cooled, the tetrahydrofuran is removed, and the aqueous phase is extracted with dichloromethane. The organic layer is dried and concentrated and the residue is chromatographed on 200 g. of silica gel. The column is eluted with 1 l. of 35% ethyl acetate-benzene and 1 l. of 40% ethyl acetate-benzene, collecting 30-ml. fractions. Those fractions containing the Formula-XXXVIII compound, in its isomeric erythro and threo forms, free of starting material and impurities, are combined and concentrated.

C. Title compound.—To a solution of the Formula-XXXVIII dihydroxy compound (step B, above, 0.8 g.) in 10 ml. of pyridine, cooled to 0°, is added 1.2 ml. of methanesulfonyl chloride. The reaction mixture is stirred for 2 hrs. and 20 g. of ice is added. The mixture is extracted with ether-dichloromethane (1:1) and the organic layer is washed successively with dilute hydrochloride acid, water, saturated aqueous sodium bicarbonate, and brine, dried, and concentrated. The residue, containing the bismesylate, is treated with 15 ml. of acetone and 10 ml. of water and stirred for 8—16 hrs. at 25°. The acetone is removed in vacuo and the remaining solution is extracted with dichloromethane. The extract is dried and concentrated and the residue is chromatographed on 150 g. of silica gel using 500 ml. ethyl acetate followed by 3% methanol ethyl acetate as eluting solvent while collecting 30-ml. fractions. Those fractions containing the Formula-XL product, free of starting material and impurities, are combined and concentrated to give the title compound; principle NMR spectral peaks at 6.57—7.3 (multiplet); 5.42—5.65 (multiplet); 4.60 (singlet) and 3.76 (singlet) δ.

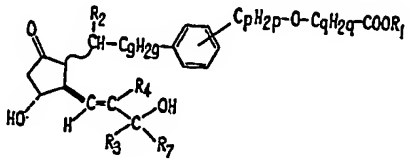
Example 32

Natural Configuration 3 - Oxa - 3,5 - *inter* - *o* - phenylene - 4 - nor - $PGF_{1\alpha}$ Methyl Ester (Formula XVII: C_eH_{2e} is ethylene; C_pH_{2p} is a valence bond in ortho relationship to C_gH_{2g}; C_cH_{2q} is methylene; G is n-pentyl; R_1 is methyl; R_2, R_3, and R_4 are hydrogen; and ~ is alpha for the carboxyl-containing moiety and for the ring hydroxyl).

Refer to Chart A. Following the procedure of Example 4, the Formula-XIII PGE_1-type compound of Example 31 is transformed to the title compound; principle NMR spectral peaks at 6.57—7.3 (multiplet); 5.33—5.56 (multiplet); 4.62 (singlet) and 3.75 (singlet) δ.

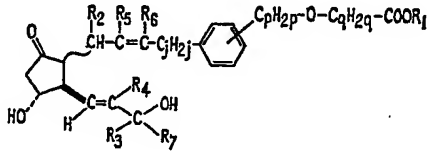
WHAT WE CLAIM IS:—

1. A compound of the formula:



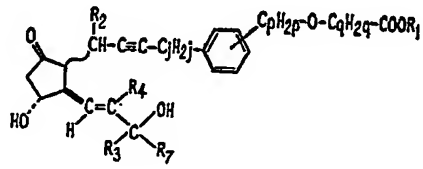
wherein R_1 is hydrogen, alkyl of one to 8 carbon atoms, inclusive, cycloalkyl of 3 to 10 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, phenyl substituted with one, 2, or 3 chloro or alkyl of one to 4 carbon atoms, inclusive, or ethyl substituted in the β-position with 3 chloro, 2 or 3 bromo, or 1, 2, or 3 iodo; wherein R_2, R_3, and R_4 are hydrogen or alkyl of one to 4 carbon atoms, inclusive; wherein C_gH_{2g} represents a valence bond or alkylene of one to 8 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between $-CHR_2-$ and the ring; wherein C_pH_{2p} represents a valence bond or alkylene of one to 6 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between the ring and the —O—; wherein C_qH_{2q} represents alkylene of one to 6 carbon atoms, inclusive, with one, 2, or 3 carbon atoms between —O— and $-COOR_1$; wherein C_gH_{2g}, C_pH_{2p}, and C_qH_{2q} together represent one to 20 carbon atoms, inclusive, with total chain lengths one to 5 carbon atoms, inclusive; wherein R_7 is hydrogen, alkyl of one to 10 carbon atoms, inclusive, substituted with zero, one, 2, or 3 fluoro, or alkyl of 2 to 10 carbon atoms, inclusive, substituted with 4 or 5 fluoro on the omega and omega-minus-one carbon atoms; and wherein $\sim$ indicates attachment of the group to the ring in alpha or beta configuration; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

2. A compound of the formula:



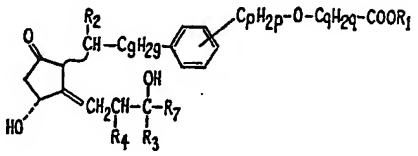
wherein R_1, R_2, R_3, R_4, R_7 and $\sim$ are as defined in claim 1; wherein R_5 and R_6 are hydrogen or alkyl of one to 4 carbon atoms, inclusive; wherein C_jH_{2j} represents a valence bond or alkylene of one to 5 carbon atoms, inclusive, with one or 2 carbon atoms between $=CR_6-$ and the ring with the proviso that the total carbon-atom content of $-CR_5=CR_6-C_jH_{2j}-$ does not exceed 8; wherein C_pH_{2p} represents a valence bond or alkylene of one to 6 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between the ring and the —O—; wherein C_qH_{2q} represents alkylene of one to 6 carbon atoms, inclusive, with one, 2, or 3 carbon atoms between —O— and $-COOR_1$; wherein C_jH_{2j}, C_pH_{2p}, and C_qH_{2q} together represent one to 17 carbon atoms, inclusive, with total chain lengths one to 3 carbon atoms, inclusive; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

3. A compound of the formula:



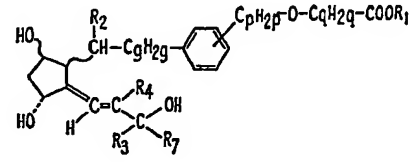
wherein R_1, R_2, R_3, R_4, R_7 and ~ are as defined in claim 1; wherein C_jH_{2j} represents a valence bond or alkylene of one to 5 carbon atoms, inclusive, with one or 2 carbon atoms between —C≡C— and the ring; wherein C_pH_{2p} represents a valence bond or alkylene of one to 6 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between the ring and the —O—; wherein C_qH_{2q} represents alkylene of one to 6 carbon atoms, inclusive, with one, 2, or 3 carbon atoms between —O— and —$COOR_1$; wherein C_jH_{2j}, C_pH_{2p}, and C_qH_{2q} together represent one to 17 carbon atoms, inclusive, with total chain lengths one to 3 carbon atoms, inclusive; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

4. A compound of the formula:



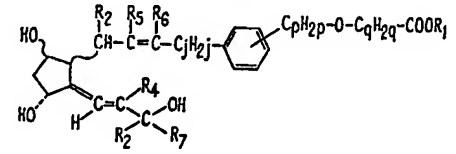
wherein R_1, R_2, R_3, R_4, R_7, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

5. A compound of the formula:



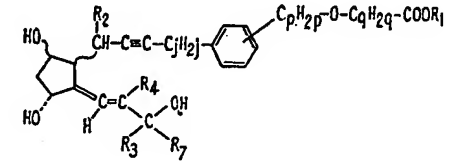
wherein R_1, R_2, R_3, R_4, R_7, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

6. A compound of the formula:



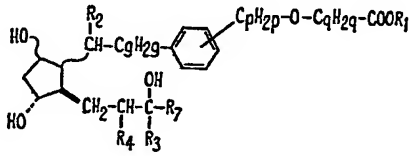
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 2; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

7. A compound of the formula:



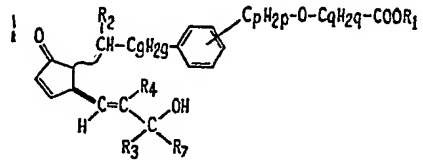
wherein R_1, R_2, R_3, R_4, R_7, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 3; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

8. A compound of the formula:



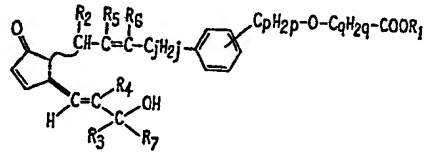
wherein R_1, R_2, R_3, R_4, R_7, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

9. A compound of the formula:



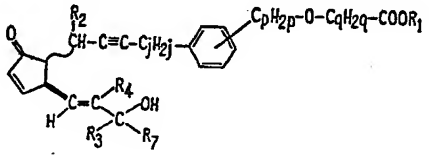
wherein R_1, R_2, R_3, R_4, R_7, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

10. A compound of the formula:



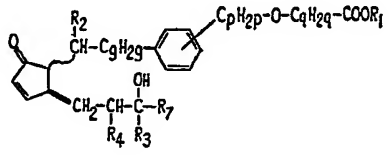
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, C_jH_{2j}, C_pH_{2p}, C_gH_{2g} and ~ are as defined in claim 2; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

11. A compound of the formula:



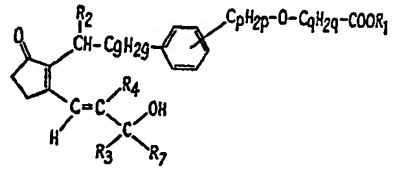
wherein R_1, R_2, R_3, R_4, R_7, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 3; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

12. A compound of the formula:



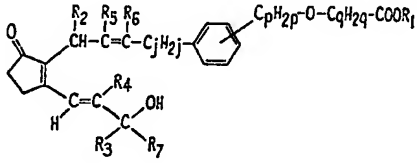
wherein R_1, R_2, R_3, R_4, R_7, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ and as defined in claim 1; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

13. A compound of the formula:



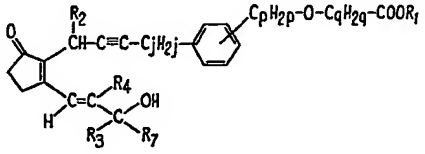
wherein R_1, R_2, R_3, R_4, R_7, C_gH_{2g}, C_pH_{2p} and C_qH_{2q} are as defined in claim 1; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

14. A compound of the formula:



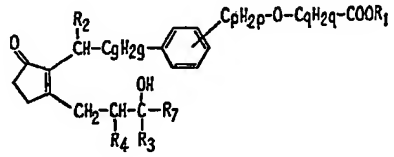
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, C_jH_{2j}, C_pH_{2p} and C_qH_{2q} are as defined in claim 2; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

15. A compound of the formula:



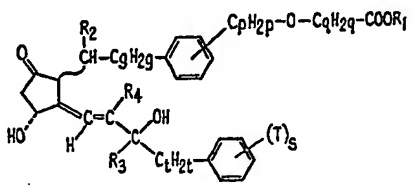
wherein R_1, R_2, R_3, R_4, R_7, C_jH_{2j}, C_pH_{2p} and C_qH_{2q} are as defined in claim 3; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

16. A compound of the formula:



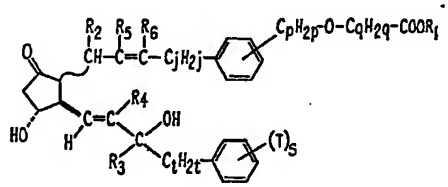
wherein R_1, R_2, R_3, R_4, R_7, C_gH_{2g}, C_pH_{2p} and C_qH_{2q} are as defined in claim 1; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

17. A compound of the formula:



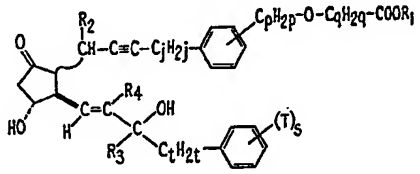
wherein R_1, R_2, R_3, R_4, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; wherein C_tH_{2t} represents a valence bond or alkylene of one to 10 carbon atoms, inclusive, substituted with zero, one, or 2 fluoro, with one to 7 carbon atoms, inclusive, between $-CR_3OH-$ and the ring; wherein T is alkyl of one to 4 carbon atoms, inclusive, fluoro, chloro, trifluoromethyl, or $-OR_9$, wherein R_9 is hydrogen alkyl of one to 4 carbon atoms, inclusive, or 2-tetrahydropyranyl and s is zero, one, 2, or 3, with the proviso that not more than two T are other than alkyl; and when two or three T's are present as substituents they may be the same or different including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

18. A compound of the formula:



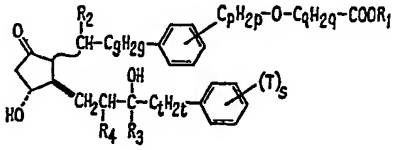
wherein R_1, R_2, R_3, R_4, R_5, R_6, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 2; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

19. A compound of the formula:



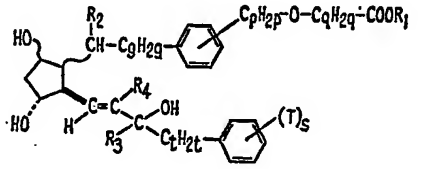
wherein R_1, R_2, R_3, R_4, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 3; T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

20. A compound of the formula:



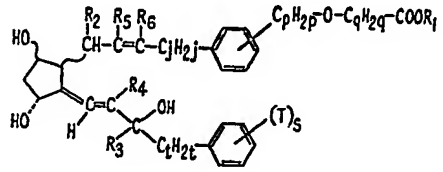
wherein R_1, R_2, R_3, R_4, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

21. A compound of the formula:



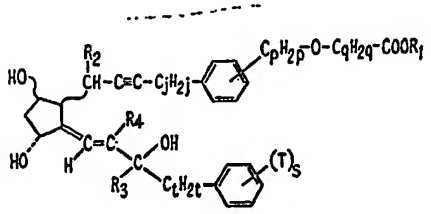
wherein R_1, R_2, R_3, R_4, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

22. A compound of the formula:



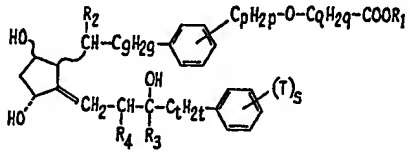
wherein R_1, R_2, R_3, R_4, R_5, R_6, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 2; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

23. A compound of the formula:



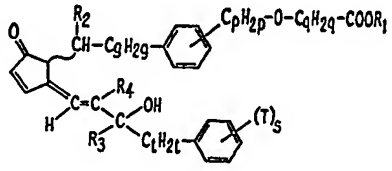
wherein R_1, R_2, R_3, R_4, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 3; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

24. A compound of the formula:



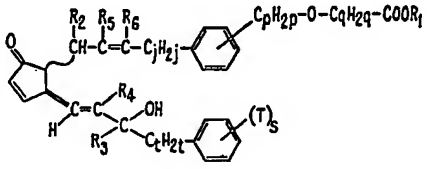
wherein R_1, R_2, R_3, R_4, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

25. A compound of the formula:



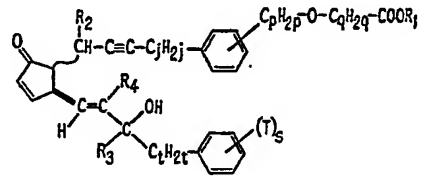
wherein R_1, R_2, R_3, R_4, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

26. A compound of the formula:



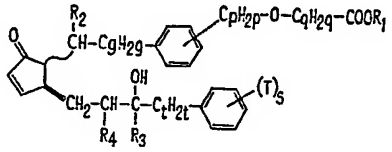
wherein R_1, R_2, R_3, R_4, R_5, R_6, C_jH_{2j}, C_pH_{2p}, C_tH_{2t} and ~ are as defined in claim 2; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

27. A compound of the formula:



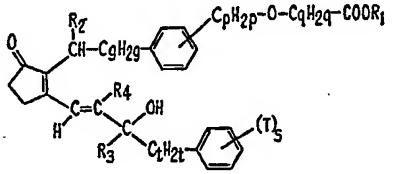
wherein R_1, R_2, R_3, R_4, C_jH_{2j}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 3; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

28. A compound of the formula:



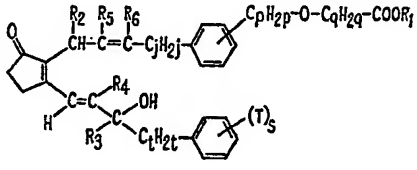
wherein R_1, R_2, R_3, R_4, C_gH_{2g}, C_pH_{2p}, C_qH_{2q} and ~ are as defined in claim 1; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

29. A compound of the formula:



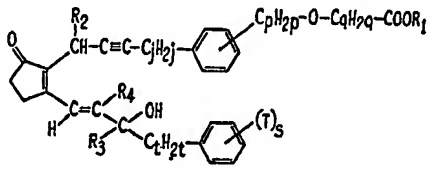
wherein R_1, R_2, R_3, R_4, C_gH_{2g}, C_pH_{2p} and C_qH_{2q} are as defined in claim 1; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

30. A compound of the formula:



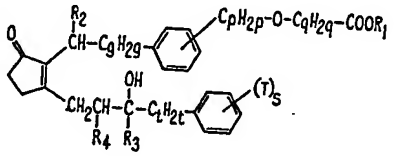
wherein R_1, R_2, R_3, R_4, R_5, R_6, C_jH_{2j}, C_pH_{2p} and C_qH_{2q} are as defined in claim 2; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

31. A compound of the formula:



wherein R_1, R_2, R_3, R_4, C_jH_{2j}, C_pH_{2p} and C_qH_{2q} are as defined in claim 3; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

32. A compound of the formula:



wherein R_1, R_2, R_3, R_4, C_gH_{2g}, C_pH_{2p} and C_qH_{2q} are as defined in claim 1; wherein C_tH_{2t}, T and s are as defined in claim 17; including the lower alkanoates thereof, and the pharmacologically acceptable salts thereof when R_1 is hydrogen.

33. dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - PGE_1 methyl ester.

34. dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - 15 - beta - PGE_1 methyl ester.

35. dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\alpha}$ methyl ester.

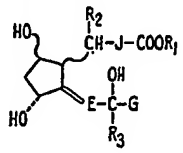
36. dl - 3 - Oxa - 3,7 - *inter* - *m* - phenylene - 4,5,6 - trinor - $PGF_{1\beta}$ methyl ester.

37. dl-3-Oxa-3,7-*inter*-*m*-phenylene-4,5,6-trinor-PGA_1.

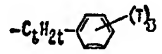
38. dl-3-Oxa-4,7-*inter*-*o*-phenylene-5,6-dinor-PGF_1 ester.

39. dl - 3 - Oxa - 4,7 - *inter* - *o* - phenylene - 5,6 - dinor - 15 - beta - PGE_1 ethyl ester.

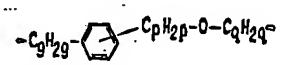
40. A process for producing a compound of the formula:



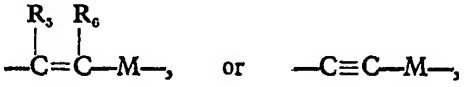
wherein G is hydrogen; alkyl of one to 10 carbon atoms, inclusive, substituted with zero, one, 2, or 3 fluoro; alkyl of 2 to 10 carbon atoms, inclusive, substituted with 4 or 5 fluoro on the omega and omega-minus-one carbon atoms; or a monovolent radical of the formula



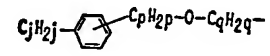
wherein C_tH_{2t}, T and s are as defined in claim 17; wherein E is $-CH_2CHR_4$ or *trans* $-CH=CR_4$, when J is



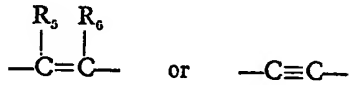
or E is *trans*- $-CH=CR_4$ when J is *cis* or *trans*



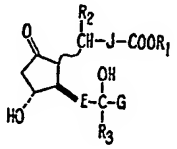
wherein C_gH_{2g} represents a valence bond or alkylene of one to 8 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between $—CHR_2—$ and the ring; wherein C_pH_{2p} represents a valence bond or alkylene of one to 6 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between the ring and the —O—; wherein C_qH_{2q} represents alkylene of one to 6 carbon atoms, inclusive, with one, 2, or 3 carbon atoms between —O— $—COOR_1$; wherein C_sH_{2s}, C_pH_{2p}, and C_qH_{2q} together represent one to 20 carbon atoms, inclusive, with total chain lengths one to 5 carbon atoms, inclusive; wherein M is



wherein C_jH_{2j} represents a valence bond or alkylene of one to 5 carbon atoms, inclusive, with one or two carbon atoms between

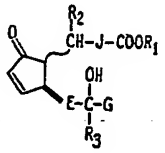


and the ring with the proviso that the total carbon content of $—CH_5=CR_6—C_jH_{2j}$ does not exceed 8, and wherein C_jH_{2j}, C_pH_{2p}, and C_qH_{2q} together represent one to 17 carbon atoms, inclusive, with total chain lengths one to 3 carbon atoms, inclusive; wherein R_1, R_2, R_3, R_4, R_5, R_6 and ~ are as defined in claim 2; which comprises reacting a compound of the formula:

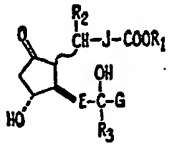


wherein E, G, J, R_1, R_2, R_3, and ~ are as defined above with a carbonyl reducing agent which does not react with ester or acid groups or ethylenic or aceptylenic linkages.

41. A process for producing a compound of the formula:

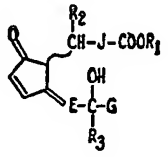


wherein E, G, J, R_1, R_2, R_3 and ~ are as defined in claim 40; which comprises acidic dehydration of the compound of the formula:

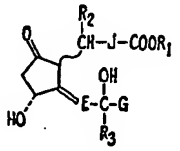


wherein E, G, J, R_1, R_2, R_3, and ~ are as defined above.

42. A process for producing a compound of the formula:

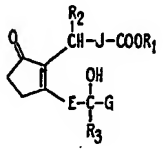


wherein E, G, J, R_1, R_2, R_3 and ~ are as defined in claim 40; which comprises dehydrating a compound of the formula:

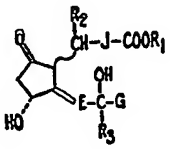


wherein E, G, J, R_1, R_2, R_3, and ~ are as defined above, with at least an equivalent amount of a carbodiimide and a catalytic amount of a copper L117 salt.

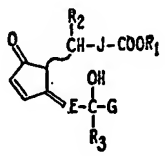
43. A process for producing a compound of the formula:



wherein E, G, J, R_1, R_2, R_3 are as defined in claim 40; which comprises reacting a compound of the formula:

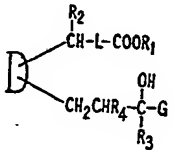


or

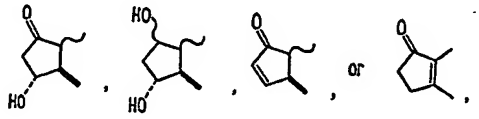


wherein E, G, J, R_1, R_2, and R_3 are as defined above, and ~ indicates attachment of the group to the ring in alpha or beta configuration, with a base whose aqueous solution has pH greater than 10.

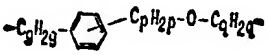
44. A process for producing a compound of the formula:



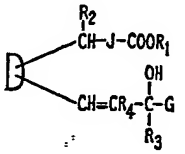
wherein D is one of the four carbocyclic radicals:



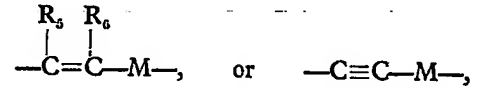
wherein G_1, R_1, R_2, R_3 and ~ are as defined in claim 40; wherein L is



wherein C_gH_{2g} represents a valence bond or alkylene of one to 8 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between —CHR_2— and the ring; wherein C_pH_{2p} represents a valence bond or alkylene of one to 6 carbon atoms, inclusive, with one, 2, 3, or 4 carbon atoms between the ring and the —O—; wherein C_qH_{2q} represents alkylene of one to 6 carbon atoms, inclusive, with one, 2, or 3 carbon atoms between —O— and —$COOR_1$; wherein C_gH_{2g}, C_pH_{2p}, and C_qH_{2q} together represent one to 20 carbon atoms, inclusive, with total chain lengths one to 5 carbon atoms, inclusive; which comprises reducing a compound of the formula:

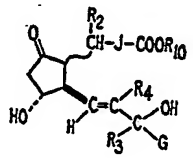


wherein D, G, R_1, R_2, R_3, and R_4 are as defined above; and wherein J includes L as defined above, *cis* or *trans*



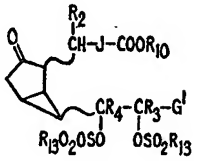
wherein M is as defined in claim 40.

45. A process for preparing a compound of the formula:



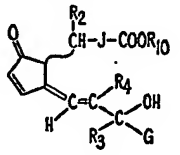
wherein G, R_2, R_3, R_4, J and ~ are as defined in claim 40; wherein R_{10} is alkyl of

one to 8 carbon atoms, inclusive, cycloalkyl of 3 to 10 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, phenyl substituted with one, 2 or 3 chloro or alkyl of one to 4 carbon atoms, inclusive, or ethyl substituted in the β-position with 3 chloro, 2 or 3 bromo, or 1, 2, or 3 iodo; which comprises reacting a compound of the formula:

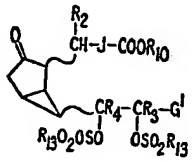


wherein J, R_2, R_3, R_4, and R_{10} are as defined above; wherein G is the same as G defined above except that R_9 is not hydrogen; wherein R_{13} is alkyl of one to 5 carbon atoms, inclusive; and wherein $\sim$ indicates attachment of a group to the cyclopentane ring in alpha or beta configuration, and to the cyclopropane ring in *exo* or *endo* configuration; with water in the range 0° to 60° C.

46. A process for producing a compound of the formula:

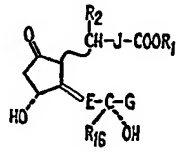


wherein G, J, R_2, R_3, R_4, R_{10} and $\sim$ are as defined in claim 45; which comprises reacting a compound of the formula:

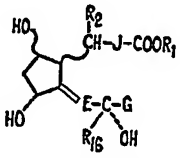


wherein J, R_2, R_3, R_4, and R_{10} are as defined above; wherein G is the same as G defined above except that R_9 is not hydrogen; wherein R_{13} is alkyl of one to 5 carbon atoms, inclusive; and wherein $\sim$ indicates attachment of a group to the cyclopentane ring in alpha or beta configuration, and to the cycloprane ring in *exo* or *endo* configuration; with a combination of water, a base characterized by its water solution having a pH 8 to 12, and sufficient water-soluble organic diluent to form a basic substantially homogeneous reaction mixture in the range of 40 to 100°C.

47. A process for producing a compound of the formula:

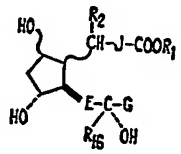


wherein E, G, J, R_2, R_1 and $\sim$ are as defined in claim 40; wherein R_{16} is alkyl of one to 4 carbon atoms, inclusive, which comprises reacting a compound of the formula:

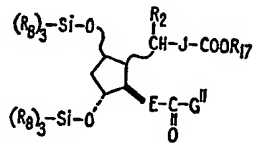


wherein E, G, J, R_1, R_2, R_{16}, and $\sim$ are as defined above; with an oxidizing agent which selectively oxidizes secondary hydroxy groups to carbonyl groups.

48. A process for producing a compound of the formula:



wherein E, G, J, R_1, R_2, R_{16} and ~ are as defined in claim 47; and wherein R_{16} and the —OH group on —CR_{16}— are in either α or β configuration; which comprises the steps of (a) reacting a compound of the formula:



wherein E, J, R_2, and ~ are as defined above; R_8 is alkyl of one to 4 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, or phenyl substituted with one or 2 fluoro, chloro or alkyl of one to 4 carbon atoms, inclusive; R_{17} is R_1 as defined above or silyl of the formula —Si—$(R_8)_3$ wherein R_8 is as defined above; and G'' is the same as G above except that, in R_9, —$Si(R_8)_3$ replaces hydrogen; with a Grigrard reagent of the formula $R_{16}MgHal$ wherein R_{16} is alkyl of one to 4 carbon atoms, inclusive and Hal is chloro, bromo, or iodo; (b) hydrolyzing the Grignard complex; and (c) hydrolyzing the resulting silylated tertiary alcohol to remove the silyl groups.

49. 3-Oxa-3,5-*inter-o*-phenylene-4-nor-PGE_1 methyl ester.

50. 3-Oxa-3,5-*inter-o*-phenylene-4-nor-$PGE_{1\alpha}$ methyl ester.

51. A process for the preparation of a compound as claimed in any of claims 1 to 39, 49 and 50 substantially as herein described with reference to the Examples.

52. A compound as claimed in any of claims 1 to 39, 49 and 50 when prepared by a process as claimed in claims 40 to 48 and 51.

53. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 1 to 39 or 49, 50 or 52 together with a pharmaceutically acceptable carrier.

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